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Biocompatibility and fixation properties of absorbable miniplates and screws in growing calvarium

An experimental study in sheep

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Academic dissertation

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LIST OF ORIGINAL PUBLICATIONS

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I Peltoniemi HH, Tulamo RM, Pihlajamäki HK, Kallioinen M, Pohjonen T, Törmälä P, Rokkanen PU, Waris T. Consolidation of craniotomy lines after resorbable polylactide and titanium plating: a comparative experimental study in sheep. Plast Reconstr Surg 101:123-33, 1998

II Peltoniemi HH, Ahovuo J, Tulamo RM, Törmälä P, Waris T. Biodegradable and titanium plating in experimental craniotomies: a radiographic follow-up study. J Craniofac Surg 8 (No 6):446-51; discussion 452-3, 1997

III Peltoniemi HH, Tulamo RM, Toivonen T, Pihlajamäki HK, Pohjonen T, Törmälä P, Waris T. Intraosseous plating: a new method for biodegradable osteofixation in craniofacial surgery. J Craniofac Surg 9 (No 2):171-176; discussion 9 (No 3):247, 1998

IV Peltoniemi HH, Hallikainen D, Toivonen T, Helevirta P, Waris T. SR-PLLA and SR-PGA miniscrews: biodegradation and tissue reactions in the calvarium and dura mater. J Craniomaxillofac Surg 27(1):42-50, 1999

V Peltoniemi HH, Tulamo RM, Toivonen T, Hallikainen D, Törmälä P, Waris T. Biodegradable semirigid plate and miniscrew fixation in experimental calvarial osteotomies: A comparative study with rigid titanium fixation. J Neurosurg 90:910-917, 1999

ABBREVIATIONS

A	surface area (in mechanical studies)
AO	Arbeitsgemeinschaft für Osteosynthesefragen
AP	anteroposterior
bwt	body weight
CRP	C-reactive protein
CT	computerized tomography
DSC	differential scanning calorimetry
EM	electron microscopy
F	force
FBR	foreign-body reaction
FOV	field of view
GBR	guided bone regeneration
GPa	giga Pascal (10^9 N/m^2)
Gy	Gray
HMM	histomorphometry
hmw	high molecular weight
HU	Hounsfield Unit
im	intramuscular
IU	international unit
iv	intravenous
MMF /mmf	maxillo-mandibular fixation
MPa	mega Pascal (10^6 N/m^2)
MRI	magnetic resonance imaging
Mv	viscosity average molecular weight (g/mol)
Mw	weight-average molecular weight (g/mol)

N	newton
n	number
OSF	osteoid surface fraction
OTC	oxytetracycline
Pa	Pascal (N/m^2)
PDLA	poly-D-lactide
PDLLA	poly-DL-lactide (50:50)
PDS	polydioxanon
PGA	polyglycolic acid or polyglycolide
PLA	polylactic acid or polylactide
PLA96	poly-L,D-lactide (96% L-lactide, 4% D-lactide)
PLA 85/15	poly-L,D-lactide (85% L-lactide, 15% D-lactide) (=70% L-lactide, 30% DL-lactide)
P(L/DL)LA	poly-L,DL-lactide
P(L/DL)LA 70/30	poly-L,DL-lactide (70% L-lactide, 30% DL-lactide)
PLGA	copolymer of polylactide and polyglycolide
PLGA70/30	copolymer of polylactide and polyglycolide (70% polylactide, 30% polyglycolide)
PLLA	poly-L-lactide
sc	subcutaneous
SEM	scanning electron microscopy
SR	self-reinforced
Tg	glass transition temperature (°C)
Tm	melting temperature (°C)
Ti	titanium

INTRODUCTION

Since Paul Tessier´s revolutionary innovation, congenital craniofacial skeletal malformations have generally been treated in infancy by extensive operative procedures, where skull bones are taken to pieces and reconstructed. The desired shape and space are secured by internal fixation (*Jackson et al.* 1982). The development of rigid metallic mini- and microfixation techniques in the 1980´s radically improved many surgical techniques, and the materials were readily transferred from adult craniofacial surgery to paediatric use (*Mühlbauer et al.* 1987; *Sadove and Eppley* 1991). However, a growing dynamic human neurocranium sets special requirements for osteosynthesis materials. In 1995, the first report on passive intracranial translocation of metallic plates and screws was published (*Fearon et al.* 1995), followed by several others (*Goldberg et al.* 1995a; *Honig et al.* 1995; *Yu et al.* 1996). Passive intracranial translocation carries a potential risk of brain damage and impedes further operations. Metallic internal fixation devices have also proved to restrict the growth of the neurocranium (*Yaremchuk* 1994) and cause scatter in CT and MRI investigations (*Sullivan et al.* 1994), which is of particular concern in intracranial areas immediately adjacent to the osteosynthesis devices.

The risks associated with metallic mini- and microfixation devices used in paediatric craniofacial surgery and the need of a subsequent removal operation have given a rise to the development of biodegradable mini-osteosynthesis devices. Devices made of polylactic acid (PLA) and polyglycolic acid (PGA) and their copolymers have been used in the internal fixation of fractures and osteotomies in orthopaedic surgery since 1980´s after extensive experimental studies (*Rokkanen et al.* 1996). Cutright et al. started the development of biodegradable fracture fixation devices in the field of maxillofacial surgery in 1971 (*Cutright et al.* 1971), followed by various experiments in the maxillofacial area (*Suuronen* 1993). Illi et al. were the first to use resorbable polydioxanone bands for fixation of calvarial osteotomies (*Illi et al.* 1989). The obvious biocompatibility of certain resorbable materials and the urgent need of alternative methods to metallic fixation led to a rapid change-over to biodegradable fixation in non-loaded osteosyntheses in the infant neurocranium after 1995.

Weakness of the materials was the major limiting factor in the manufacture of mini implants in the 1980´s. Bulky, highly crystalline PLLA implants caused foreign-body reactions (*Bergsma et al.* 1993), which cast a shadow on all biodegradable implants. The self-reinforcing technique, invented by the Finnish professors Rokkanen and Törmälä, enables the manufacture of large, extremely strong orthopaedic implants and thin, delicate, but strong mini implants (*Törmälä* 1992; *Rokkanen et al.*

1996). The new generation of SR-implants has been used clinically in correction of craniofacial malformations in children (*Waris et al.* 1995) and in adult maxillofacial surgery (*Haers et al.* 1998; *Suuronen et al.* 1998a).

Because of the rapid formation and healing of bone in infants, as a result of the osteogenicity of infant dura, only a short period of biomechanical stability is required. Polymer type and plate size must be carefully tailored to the dynamics of the skeletal site (*Eppley and Sadove* 1992; *Antikainen* 1993). The effects of applied strain from extensive three-dimensional bone growth as in rapidly growing infants may hasten the degradation process of the implants (*Eppley and Sadove* 1995a). In addition, craniofacial remodelling operations commonly result in small or even large bone defects, which may not consolidate as completely as has been assumed previously (*Prevot et al.* 1993), and which set special requirements as regards implants. The histological demonstration of complete device resorption without adverse local tissue effects in thin calvarial bone is important before clinical use because incomplete polymer elimination may eventually be associated with chronic inflammatory tissue changes (*Bergsma et al.* 1995).

Thus, experiments in large mammals are needed to study the effects of these materials on the osseous healing process of membranous calvarial bone osteotomies and the biocompatibility and bioabsorption processes of the materials. In these less loaded areas, a bioabsorbable method of fixation could be an alternative to rigid metallic fixation methods in correction of congenital malformations and in tumour and trauma surgery.

REVIEW OF THE LITERATURE

Development and growth of the human calvarium

The human skull consists of the bony neurocranium enveloping and protecting the brain and the viscerocranium constituting the facial bones. The neurocranium consists of the concave calvarium and the cranial base. The bones of the calvarium and most of the facial bones are membranous bones which are derived directly from mesenchymal tissues (*Enlow* 1990). They differ from endochondral bones in their way of growing and healing. During early intrauterine phases of development, the brain is surrounded by a mesenchymal capsule. This precursor of the dura mater becomes folded in areas where different parts of the brain arch against each other (*Smith and Tondury* 1978). These folds later serve as the basal origins of the cranial sutures. Most of the osseous calvarium is formed directly from the mesenchymal capsule by intramembranous ossification (*Smith and Tondury* 1978). At the time of birth all the calvarial bones (frontal, temporal, parietal and occipital) are present as fibrous plates with centres of maturing bone. Membranous bones grow by membranous ossification in conjunction with the periosteal and endosteal (dura) membranes (*Enlow* 1990). Ossification proceeds rapidly during the first postnatal year, and finally the bone centers become bone plates, now calvarial bones, which come into intimate contact through fibrous sutures (*Friede* 1981). Sutures are complexes of cellular and fibrous tissue which unite bones, absorb forces, act as joints by permitting some movement of adjacent bones and act as growth sites in the growing skull (*Wagemans et al.* 1988).

During perinatal and early postnatal life, the rapid volume increase of the brain stimulates growth, development and molding of the skull (*Enlow* 1990). The brain and cranial vault reach approximately 75 percent of their eventual adult size by 3 years and 90 percent by 5 years of age (*Waitzman et al.* 1992). As the brain grows it pushes the cranial bone plates apart. This leads to tension in membranous layers (periosteum and dura) and sutures, and bone reacts by depositing bone in the bone margins next to sutures. A very important mechanism in the growth and remodellation of calvarium is deposition of new bone on the outer surface and resorption on the inner surface. When growing cranial bone encounters a rigid structure, it moves around it through deposition and resorption, which results in a relative change in the position of for example a rigid plate ("passive translocation") (*Jackson et al.* 1982; *Enlow* 1990).

Regeneration and consolidation of calvarial (membranous) bone

The effects of surgical manipulation on regeneration of cranial bone

Thermal damage during bone preparation leads to cell death and bone necrosis. The extent of surgical trauma (*Albrektsson* 1980a) and ischaemia (*Albrektsson* 1982) also have an effect on bone healing. Neither osteogenesis nor resorption of bone will occur before vascularization of the bone (*Albrektsson* 1980b). A membranous bone graft undergoes a process similar to that seen with aseptic necrosis, i.e., resorption of necrotic bone (*Manson* 1994), the bone graft becoming a combination of living cells and dead bone, with the graft finally being replaced by new bone within 10 weeks (*Thaller et al.* 1996). Surgical procedures themseves have been shown to have a deleterious effect on frontal bone development: removing the frontal bones of rabbits by craniotomy and replacing them as free grafts (with wire osteosynthesis) reduced their anteroposterior growth potential by 10% (*Polley et al.* 1995).

Role of the dura in regeneration of cranial bone

Dural continuity has been considered of major importance for bone regeneration experimentally (*Sirola* 1960). An experimental study on 2 to 3-week-old rabbits showed that regeneration of parietal bone defects was much greater than in adult rabbits, especially when the overlying periosteum and dura were preserved, and bony regeneration was greater in the absence of periosteum provided that the dura was present (*Reid et al.* 1981). Another study with isogeneic guinea pigs demonstrated that only infant dura was capable of supporting complete or near complete bone regeneration of surgically created calvarial defects. Adult dura and periosteum lacked such osteogenic properties (*Hobar et al.* 1993; *Hobar et al.* 1996). In 6-week old rabbits, bone deposition leading to calvarial redevelopment was directly dependent upon the presence of the dura mater, and the rate of deposition was apparently affected by dural continuity, animal age, and localized differences in the thickness of the dural layers (*Mossaz and Kokich* 1981).

In the literature, lack of ossification after cranial remodelling in children has seldom been considered with few exceptions. Poor osseous wound healing has been reported in 6.3% of children aged 2-11 months at the time of surgery (*Prevot et al.* 1993). Main explanations have included local postoperative infection (75% of all affected cases), forehead advancement especially in association with resorbable suture osteosynthesis, and brachycephaly. Repaired tears of the dura mater do not appear to pose a risk. Tears of the dura mater, if left unrepaired, may contribute to incomplete ossification (*Powiertowski and Matlosz* 1970; *Prevot et al.* 1993), and expanding cranial bone defects and brain herniation (*Winston et al.* 1983; *Muhonen et al.* 1995; *Umansky and Schendel* 1995).

Role of the periosteum in regeneration of cranial bone

Cutting et al. demonstrated that the outer surface of the calvaria receives blood dif-

fusely from the periosteum (*Cutting et al.* 1984). They also reported an increased surviving volume of calvarial bone following vascularized transfer versus a traditional nonvascularized bone graft, which was periosteally covered. The role of the periosteum thus seems to be important when its blood supply is preserved, but its role is minor or nonexistent if it is not preserved (*Cutting and McCarthy* 1983). The role of periosteum has been considered to be of greater importance than dura in adult age (*Gosain and Persing* 1999). In cases of forehead advancement, although periosteal flaps are preserved and replaced on the reshaped skull, they are often not large enough at the end of the operation to cover the whole vault, which may also contribute to incomplete ossification (*Prevot et al.* 1993). In vascularized bone grafts, periosteum provides a surviving population of osteogenic cells and route for early revascularization, whereas free grafts are characterized by significant resorption and a delay in subperiosteal bone formation (*Antonyshyn et al.* 1987).

Guided bone regeneration

In numerous studies, guided bone regeneration (GBR) has been demonstrated to be effective in osteoconduction and prevention of fibrous nonunions in craniofacial bone defects (*Gottlow* 1984; *Dahlin et al.* 1988; *Dahlin et al.* 1991; *Gottlow et al.* 1993; *Karring et al.* 1993; *Linde et al.* 1993; *Lundgren et al.* 1995; *Hutmacher et al.* 1996; *Lemperle et al.* 1998). In GBR, a membrane is positioned to "exclude" rapidly colonizing fibroblastic cells from a wound site during healing, and "guide" more slowly migrating osseous cells into the wound site, resulting in direct bony regeneration and deposition (*Linde et al.* 1993).

If a bone defect exists between the bone margins, rigid fixation with membrane covering the bone defect shows most rapid and organized osseous wound healing when compared with non-rigid or non-covering fixation. Mooney *et al.* studied healing of 5 mm-wide zygomatic arch osteotomies in rabbits, when fixed rigidly (microplates and screws) or non-rigidly (wire fixation) and the gap covered with collagen membrane or left uncovered (*Mooney et al.* 1996). Rigidly fixed and membrane-covered defects consolidated most rapidly, followed by defects that were non-rigidly fixed but membrane-covered, the difference being statistically non-significant. The defects without membrane coverage resulted in non-union.

Periosteum alone (without any other membrane) has also been considered to function as a biologically active membrane, excluding nonosteogenic, extraskeletal tissues from the organizing clot (*Engdahl* 1971; *Linde et al.* 1993).

If a resorbable membrane or plate is used for GBR, it is essential that the implant retains integrity for a sufficient time period for bone regeneration. If degradation is too rapid or the implant too weak, osteoblasts will be deprived of a surface on which to migrate and secrete bone matrix, the result being fibrous repair rather than osseous regeneration (*Levy et al.* 1994; *Meikle et al.* 1994). In addition, too rapid resorption of the polymer may interfere with the consolidation process: during resorption of PLGA, osteoneogenesis is slowed at the implant site (*Winet and Bao* 1997).

Role of type of fixation on regeneration of cranial bone

Typically, membranous bones heal by direct bony union without callus formation, which has been shown in sagittal ramus osteotomies in monkeys (*Ellis et al.* 1992) and in calvarial bone fractures in rats (*Alberius and Johnell* 1991). Rigid fixation creates a favourable environment for direct bony deposition from stable, approximated bony osteotomy margins (*Ellis et al.* 1992). Because the membranous bone is dense in nature, new vessel ingrowth is sensitive to shearing forces, a situation which favours rigid fixation (*Phillips and Rahn* 1990).

Instability and mobility, especially associated with functional loading of non-rigidly -fixed osteotomy segments, may also retard the formation of osteogenic macromolecules, cytokines, extracellular matrix and growth factors, thus resulting in the formation of fibrous or cartilaginous connective tissue, fibrous non-unions, and subsequent osseous instability (*Ellis et al.* 1992). In areas of motion, the application of rigid fixation also improves bone graft survival, whereas in a low-motion region, no differences in graft volume retention as a function of fixation have been observed (*Lin et al.* 1990).

In long bones, rigid metallic plate fixation causes stress-shielding in the underlying cortical bone (*Uhthoff and Dubuc* 1971; *Paavolainen et al.* 1978). Protection from stress will occur in a mechanical reparative system if the plate has a higher modulus of elasticity than the bone to which it is attached. The reduction of bone mass is significant under stainless steel plates, and can be compensated for by early removal (eight weeks) of the plates (*Uhthoff and Finnegan* 1983). In loaded membranous bones, stress-shielding has also been reported (*Kennady et al.* 1989b; *Iizuka et al.* 1991a). Less rigid plating systems have shown superior healing in long bones (*Foux et al.* 1997) and in Le Fort I osteotomies in monkeys (*Calhoun et al.* 1989).

In the literature, there is only one published experimental study on fixation of unstable craniotomies with bioadegradable implants (*Illi et al.* 1990). In fixation of bone grafts, biodegradable, initially rigid fixation has been shown to permit adequate stabilization for a finite period, allowing bone graft revascularization and eliminating osteolysis (*Thaller et al.* 1996).

Rigid (metallic) fixation in craniofacial surgery

Since the 1940´s, metallic wires have been used to attach bone fragments non-rigidly, but rigid fixation with metallic miniplates and miniscrews was a major breakthrough in the development of craniofacial surgery in the 1980´s. The principle of the new operative techniques in synostosis surgery, originally developed by Paul Tessier, consisted of complete release of all the stenoses of the neuro- and viscerocranium, anatomical and physiological positioning of the skeleton, and temporary fixation with miniplates and sutures (*Mühlbauer et al.* 1987). The approach was intracranial, extranasal, and extraoral through a single coronal incision. The idea of temporary rigid fixation was to maintain the desired shape and space with bone gaps against the tractional forces of the soft tissues for 3 to 6 months, and then remove the plates through stab incisions to create a “floating

cranio-orbitofacial complex", to take optimal advantage of the formative power of the growing brain during the first 2 years of life (*Mühlbauer and Anderl* 1983; *Mühlbauer et al.* 1987). In infants, disjunction is more important than advancement, making this approach a dynamic one in contrast to the static procedures used for adults (*Mühlbauer et al.* 1987), and the use of rigid fixation in growing children was recommended to be limited to unstable bone sites (*Sadove and Eppley* 1991) and loaded conditions with bone defects, e.g., in orthognatic surgery. The advantages of rigid fixation include greater bony stability of osteotomized bone flaps and grafts, greater accuracy in bone reshaping, simplification of osteotomy design, and enhancement of primary bone healing with decreased resorption and infection rates (*Jackson et al.* 1986; *Mühlbauer et al.* 1987; *Sadove and Eppley* 1991). Hence the new methods, especially microfixation techniques, were rapidly adopted in paediatric use.

Problems associated with rigid (metallic) fixation in the growing skull

Restriction of growth

Rigid metallic plating over craniofacial sutures causes consistent asymmetry between the plated and nonplated sides, with deviation of the midline towards the plated side (*Resnick et al.* 1990; *Marschall et al.* 1991; *Wong et al.* 1991; *Wong et al.* 1993). Local restriction of growth has been documented experimentally with both metallic rigid and non-rigid wire fixation (*Lin et al.* 1991; *Yaremchuk et al.* 1994; *Polley et al.* 1995; *Polley et al.* 1998). The degree of growth restriction increases with the amount of fixation hardware used, but when the fixation devices are appropriately sized and located in non-growth centre regions, growth restriction can be limited (*Lin et al.* 1991; *Wong et al.* 1991; *Mooney et al.* 1992; *Wong et al.* 1993; *Yaremchuk et al.* 1994; *Polley et al.* 1995; *Polley et al.* 1998). Also single-point fixation within one plane, removal of rigid fixation hardware, and the use of semirigid fixation approaches can significantly reduce the long-term growth effects (*Polley et al.* 1998).

Passive translocation of metallic implants

The first reports on passive intracranial translocation of metallic hardware were published in 1995 (*Fearon et al.* 1995; *Goldberg et al.* 1995a; *Papay et al.* 1995), causing great concern and discussion (*Posnick and Yaremchuk* 1995; *Yaremchuk and Posnick* 1995; *Persing et al.* 1996). Device transposition is more likely to occur in infants (*Goldberg et al.* 1995), especially with syndromic forms of craniosynostoses, and when (long) plates are placed in temporal and lateral areas (*Goldberg et al.* 1995; *Yaremchuk and Posnick* 1995). However, any implants, even wires, may translocate (*Yaremchuk and Posnick* 1995). CT imaging demonstrated translocation of microfixation in 14 of 27 patients, who were under three years of age at the time of operation (*Goldberg et al.* 1995). Experimental studies on passive translocation have shown transposition of microplates in piglets (*Yu et al.* 1996; *Stelnicki and Hoffman*

1998) and even in adolescent minipigs (*Honig et al.* 1995). Unilateral fronto-orbital advancement and rigid fixation using microplates and screws were performed in 3-week-old pigs (*Yu et al.* 1996). At 6 months of age, 28% of microplates showed complete intracranial translocation, 27% remained on the ectocranial surface, and 44% were located between the outer and inner cortices of the calvaria. In the underlying brain and meninges, demonstrable histological alterations were demonstrated, but neither signs of cerebritis, gliosis or hypoxic change nor clinical sequelae were noticed. Implantation of titanium, Vitallium and stainless steel in the rabbit brain did not cause any behavioral changes or neurological defects as long as 26 weeks postimplantation (*Mofid et al.* 1997). Titanium and Vitallium incited a similar inflammatory response, which was less than that found with stainless steel wire.

There are no documented cases of early or late brain injury (i.e., seizures, stroke, haematoma, memory loss or infection) resulting from previously implanted internal fixation devices (*Yaremchuk and Posnick* 1995; *Goldberg et al.* 1995; *Persing et al.* 1996). Metallic materials can be incorporated into the dura and pose a difficulty in surgical reoperations (*Fearon et al.* 1995) and possibly a risk in MRI.

Other problems associated with metallic osteosynthesis materials

Metallic fixation devices may cause a distinct cosmetic deformity, palpability or wound dehiscence especially if placed under a scarred, tight scalp (*Fearon et al.* 1995). Plate exposure has been reported to be associated especially with preoperative radiotherapy (*McCann et al.* 1994). Common reasons for hardware removal have been reported to include palpable or prominent hardware (34.5% of the patients needing implant removal), loosening of plates and screws (25.5%), pain (25.5%), infection (23.6%), wound dehiscence/exposure of hardware (20%), and removal at the time of secondary procedures (9.1%) (*Orringer et al.* 1998).

Metallic devices also interfere with radiological investigations. Titanium devices have superior imaging characteristics, creating fewer computed tomographic and MR imaging artifacts and permitting better resolution of anatomical structures than other metallic devices (*Fiala et al.* 1993; *Fiala et al.* 1994; *Anastakis et al.* 1996).

Biocompatibility of titanium

Compared with other metals, titanium has been considered to be highly biocompatible and to have high corrosion resistance characteristics (*Linder et al.* 1983; *Carlsson et al.* 1986). The mechanical integrity of the oxide film that covers titanium alloys is essential for the long-term stability and survival of the implant. Combined stresses, motion and electrochemical processes occur at metal oxide film-tissue interfaces, which may lead to corrosion and release of titanium ions or particles. Experiments with laboratory animals (*Schliephake et al.* 1993b), and limited analyses of human tissues (*Rosenberg et al.* 1993; *Schliephake et al.* 1993a; *Katou et al.* 1996; *Jorgenson et al.* 1997; *Kim et al.* 1997) have indicated evidence of titanium release into local tissues. Although titanium ions may stay bound to local tissue, there is increasing recognition that they may also bind to protein moieties

that are transported in the bloodstream and lymphatics to remote organs (*Woodman et al.* 1984). In the literature, hypersensitivity reactions to titanium have been reported (*Lalor et al.* 1990). Corrosion and wear have also been suspected to induce chemical carcinogenesis (*Sunderman* 1989).

Polyglycolic and polylactic acid

Chemical background

Polylactic acid (PLA) and polyglycolic acid (PGA) are derivatives of cyclic diesters of glycolic and lactic acid from which they have been produced by ring opening polymerization, resulting in poly-alpha-hydroxy derivatives of the original acids (*Gilding and Reed* 1979). The polymers are composed of macromolecules with molecular weights typically from tens of thousands of daltons to more than 1 million daltons. A homopolymer (-AAAAAA-) is formed if only a single monomer is used, and a copolymer consists of two monomers (-ABABABA-). The properties of a copolymer are significantly different than those of homopolymers of any of its constituent monomers. The strength of a polymer depends on its microstructure. If the polymeric chains are randomly oriented in disorder and thus loosely packed, the polymer is called amorphous and it is weak. If the chains lie parallel and thus are packed tightly, the polymer is called crystalline and it is strong. Copolymers are typically formed by random polymerization (-ABAAABABBBBBABBB-), and the polymeric structure is commonly amorphous. Even crystalline homopolymers are not entirely crystalline and always contain both crystalline and amorphous regions and are best termed semicrystalline. Crystallinity results in higher tensile strength, a translucent to opaque optical quality, and birefringence when exposed to polarized light. Conversely, amorphous polymers are less rigid, potentially transparent, and exhibit no response to polarized light. Polymers exhibit a glass transition temperature (Tg), below which the polymer is solid and stiff and above which it is soft (*Pietrzak et al.* 1997).

Polyglycolic acid

Polyglycolic acid is a brownish, hard crystalline polymer melting at about 224-228° C, with a glass transition temperature of 36° C (*Törmälä et al.* 1998). It lacks a methyl group, which makes it hydrophilic and thus more susceptible to hydrolysis and faster degradation than polylactide. The oldest and best known commercial product made of PGA is Dexon® (*Frazza and Schmitt* 1971).

Polylactic acid

Polylactic acid is a pale-coloured semicrystalline polymer with a glass transition temperature of 57° C and a melting point of 174-184° C (*Vert et al.* 1981; *Hollinger and Battistone* 1986; *Törmälä et al.* 1998). The asymmetric lactic acid molecule has two stereoisomeric forms, L and D lactide (*Cutright et al.* 1974). In the human body, the L-isomer exists in carbohydrate metabolism, and the D-isomer is found in acidic milk. If the polymer consists only of the L isomer, it is called poly-L-lactic acid, PLLA, which has most commonly been

used in orthopaedic implants. If it contains both isomers, it is called stereocopolymer, poly-D,L-lactic acid, often referred to as P(L/DL)LA or PDLLA. Because of the stereoregularity of the molecules, PLLA is highly crystalline. The methyl group makes PLA hydrophobic and thus resistant to hydrolysis.

Basic principles in manufacture of implants

The two main methods of manufacturing polymeric implants in this study were melt moulding and solid state drawing. Melt moulding is the oldest method, and the implants are mechanically weak, which has been compensated for by enlarging the size of the implants. The melt moulding process can be subdivided into three methods to process implants from the melted raw material: compression moulding, injection moulding and extrusion. In the past, attempts to reinforce the weak implants led to use of carbon fibres as reinforcing elements.

The first PGA product, Dexon® thread, was manufactured by drawing the polymeric raw material into long fibres. This "drawing" technique was later used to produce fibres processed in a parallel fashion to strengthen the implants. These implants are called "oriented".

The self-reinforcing (SR) technique, invented and patented by Finnish professors Törmälä and Rokkanen, involves reinforcing the polymeric matrix with fibres of the same material (Fig. 1), which strengthens the polymer and gives it metal-like mechanical properties (*Törmälä* 1992). Unlike other composites, the chemical similarity between matrix and fibre produces superior matrix-fibre bond integrity and results

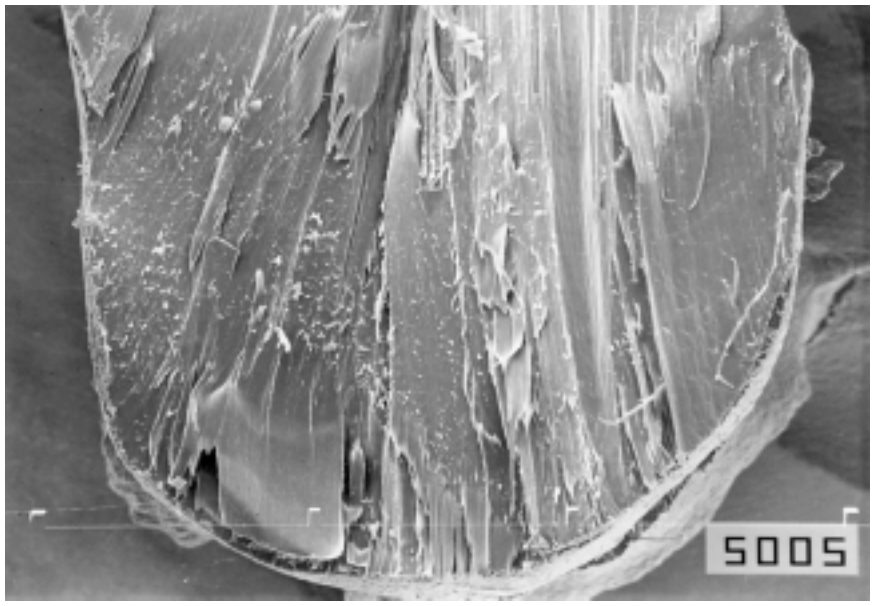


Figure 1. Scanning electron microscopy micrograph of an SR-PLLA screw with a thread diameter of 3.5 mm shows the parallel orientation of fibrils to the long axis. (Minna Kellomäki, unpublished data).

in a polymeric composite with good strength and stiffness. To manufacture screws, the self-reinforced polymer can be compression-moulded or machine-cut. The latter, new technique has improved significantly the torque and bending strengths of the screws (*Pohjonen et al.* 1997).

Biodegradation and bioabsorption of PGA and PLA implants

Bioabsorbable materials generally undergo a two-phase degradation process in the body. In the first, mainly physical phase, water molecules hydrolyse the chemical bonds of the polymer and cut long polymer chains to short chains. During this depolymerization process, the overall molecular weight and strength of the polymer become reduced and the polymer fragments. The second phase involves phagocytosis of the fragments by macrophages, and the polymer mass rapidly disappears (*Pietrzak et al.* 1997). PGA is converted hydrolytically into glycolic acid and PLA into lactic acid (Fig. 2.), which are further metabolized in the citric acid cycle to carbon dioxide and water, and the final products are excreted via respiration or urine (*Kulkarni et al.* 1966; *Brady et al.* 1973; *Williams* 1982; *Hollinger and Battistone* 1986). The degradation of PGA and PLA is accelerated *in vivo* by cellular enzymes (*Williams* 1982;*Vasenius et al.* 1990a) and free radicals (*Williams* 1992; *Ali et al.* 1993).

Hydrophilic polyglycolide degrades rapidly, whereas hydrophobic polylevolactide has a slow rate of degradation. Hydrolysis occurs initially in the amorphous regions and only later in the crystalline regions of the device. Higher amounts of crystalline structure compared with amorphous composition slow the degradation process (*Pistner et al.* 1993; *Bergsma et al.* 1995)

Any implanted device stimulates foreign-body tissue changes. After implantation of a polymeric device, the normal initial inflammatory response leads to granulation tissue enveloping the implant within one to three weeks. In early stages, polymorphonuclear leucocytes and later, macrophages, giant cells and large mononuclear cells are seen around the implant (*Kulkarni et al.* 1966; *Cutright and Hunsuck* 1971; *Getter et al.* 1972). A latent period commences and continues until the degradation and following bioabsorption by macrophages and giant cells begin. The faster the degradation process, the stronger the tissue response (*Nakamura et al.* 1989). During the most intense stage of biodegradation some patients may show clinically local fluid accumulation, which, if not treated properly by aspiration, may lead to transient sinus formation (*Törmälä et al.* 1998)

The rate of biodegradation depends on chemical composition (hydrophilic, hydrophobic), molecular weight, the degree of crystallinity, impurities (presence of residual low Mw compounds or monomers), enantiomeric purity (presence of D-isomers), sterilization (gamma irradiation vs. ethylene oxide), shape and size of the implant, site of implantation (hard or soft tissue; subcutaneously placed implants degrade faster than intraosseously implanted ones) (*Törmälä et al.* 1998), and biomechanical stresses (*Miller and Williams* 1984) to which the implant is exposed. The intensity of the tissue reaction depends on the quantity, degradation characteristics, and associated changes in the morphology of the implanted material as well as the characteristics of the tissue in which the

material is implanted.

Heterogeneity in the molecular weight, crystallinity and purity of materials, as well as lack of information on the chemical composition and/or characterization of implants has made it difficult to draw conclusions on degradation rates and biocompatibility of the materials.

Biocompatibility of PGA

Hydrophilic PGA, although highly crystalline, becomes absorbed very quickly in the body, losing virtually all strength in 6 weeks (*Vasenius et al.* 1990a) and all mass within about 3 to 12 months (*Frazza and Schmitt* 1971; *Böstman et al.* 1992a; *Thaller et al.* 1995b; *Nordström et al.* 1998). In cancellous bone tissue, biodegradation of small SR-PGA implants (2 mm pins and 3.2 mm rods) is detectable at three weeks (*Vasenius et al.* 1990b; *Nordström et al.* 1998), and in larger implants (4.5 mm screws) at six weeks (*Böstman et al.* 1992a). All these implants degraded and were absorbed completely in 24-36 weeks. During this rapid degradation, large quantities of glycolic acid monomer are released, which may locally lower the pH. The degradation of PGA is accompanied histologically by a typical non-specific foreign-body reaction (FBR) and osteolytic expansion of the implant cavity (*Böstman et al.* 1992a). FBR consists of giant cells (maximum at three to six weeks) and macrophages (maximum at 12 weeks), and scanty numbers of polymorphonuclear granulocytes and mononuclear round cells (*Päivärinta et al.* 1993). Increased osmotic pressure develops in the implant channel during degradation of the polymer which leads to transient osteolytic expansion of the implant cavity and decentralization of the polymeric particles (*Böstman et al.* 1992a).

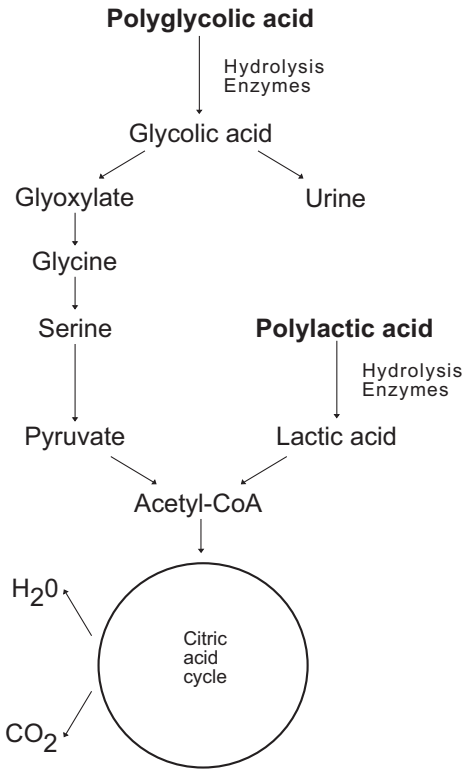


Figure 2. Biodegradation of PLA and PGA.

Transient osteolytic changes within the implant channels have been reported for instance in ankle fractures (*Böstman* 1992a; *Frokjaer and Moller* 1992) and chevron osteotomies (*Pelto-Vasenius et al.* 1997). This reaction does not affect to bony healing, and due to its transient nature, no special treatment is needed (*Pelto-Vasenius et al.* 1997). Sterile fluid accumulation has also been reported in clinical studies. Most of the clinical complications have occurred in adult patients within a few months of implantation, the time during which degradation is rapidly occurring *(Böstman et al. 1990)*. The post-operative course in 516 operated patients showed uneventful healing in 89.1%, failure of fixation in 1.2%,

bacterial wound infections in 1.7% and local fluid accumulation in 7.9%, which was treated with aspiration or incision (*Böstman et al.* 1990). The reaction is characterized by local pain, redness, swelling and oedema, but bacterial cultures are negative, and the serum concentration of CRP is low. Cytological studies on the seroma fluid have shown predominance of inflammatory monocytes and lymphocytes, thereby confirming the non-infectious nature of this infiltrate (*Santavirta et al.* 1990). Granulomatous formation of monocyte-macrophages and foreign-body giant cells has also been reported (*Böstman* 1992a). The fast degradation process of PGA, the rapid release of acidic degradation products, and the site of implantation (e.g. head of a screw located in a thin subcutaneous layer) affect the tissue responses. In distal radial fractures an incidence of clinical foreign-body reactions as high as 7/15 has been reported, when PGA rods inserted in the bone protruded far into the subcutaneous space (*Casteleyn et al.* 1992).

Biocompatibility of PLA

Excellent biocompatibility and slow biodegradation of PLA have been documented in hundreds of publications, since the first experiments: no inflammatory cell infiltrations have been reported, and foreign-body reactions have been limited to around the implanted material (*Kulkarni et al.* 1966; *Cutright et al.* 1971; *Cutright and Hunsuck* 1972).

Intraosseally implanted SR-PLLA screws and pins have been shown to cause similar, mild foreign-body reactions as corresponding metallic devices, without signs of inflammatory reactions during follow-up of 48 weeks (*Majola et al.* 1991; *Viljanen et al.* 1997). However, the resorption time of PLLA is very long, and the relatively short life expectancy of most rodents and other experimental mammals has been a problem in studying biodegradation and bioabsorption of PLLA. During degradation PLLA forms crystals, which may take 5-7 years to resorb. Matsusue *et al*. implanted ultra-high-strength PLLA rods in the femoral medullary cavity of rabbits. At 18 months histiocytes were observed; their phagocytic activity was maximal from 24 to 36 months, and at 62 months the material had been almost completely absorbed, with only a slight residual tissue reaction (*Matsusue et al.* 1995). Suuronen *et al.* fixed mandibular osteotomies in sheep with SR-PLLA multilayer plates (four 0.5-mm thick plates). After 5 years *in vivo*, the material was almost completely resorbed, but small particles of polymer could still be detected at the implantation site. However, the FBR was mainly mild (*Suuronen et al.* 1998b). Bergsma *et al.* reported a late tissue response to as-polymerized, high molecular weight (hmw) PLLA bone plates and screws used in the fixation of ten zygomatic fractures in humans (*Bergsma et al.* 1995). Their non-reinforced plates were 2 mm thick. Initial stability and fracture healing was good (*Bos et al.* 1987). Three years after implantation four patients returned because of a swelling in the operation area, and the other patients showed an identical type of swelling on recall. The 10 mm-thick swollen areas were revised 3.3 to 5.7 years postoperatively. The authors discovered remnants of degraded PLLA material digested by various cells and surrounded by a dense fibrous capsule. Histology showed FBRs without signs of inflammation. The remnants of PLLA were lying

within the macrophages, foreign-body giant cells and fibrocytes. Electron microscopy showed abundant amounts of crystal-like PLLA material, with a minimal thickness of 22 nm, internalized in the cytoplasm of various cells. They concluded that PLLA slowly degrades into particles with high crystallinity and a very slow degradation rate, but they do not cause severe cell injury or cell death. The origin of the swelling was supposed to be the increased osmotic pressure caused by these fragments and subcutaneous implantation.

Eitenmüller *et al.* used injection-moulded, non-reinforced 3-mm-thick hmw PLLA plates for fixation of ankle fractures. Fifty-two per cent of the patients demonstrated an aseptic soft tissue problem caused by delayed clearance of the degrading polylactide particles. In a second protocol, volume-reduced plates and screws did not cause any soft tissue reactions (*Eitenmüller et al.* 1996). Foreign-body reactions caused by hmw, as-polymerized PLLA material used by Bergsma and co-workers should not be generalized to cover all PLLA materials. PLLA materials may differ considerably in purity of the raw material and method of processing. Crystals were also found by Suuronen *et al.*, but, in contrast, they found no soft tissue reactions (*Suuronen et al.* 1998b).

Subcutaneously implanted PLLA plates (20 x 10 x 1 mm) were associated with mesenchymal tumours in 22 out of 50 rats. Similar non-resorbable polyethylene plates were associated with the same kind of tumours in 23 out of 50 rats (*Nakamura et al.* 1994). This is typical of the so-called Oppenheimer effect, i.e., long-term implantation of any material brings the problem of foreign-body tumourigenesis in rodents (*Oppenheimer et al.* 1955). *In vitro*, poly-L-lactide has been shown to inhibit carcinoma cell growth (*Campbell et al.* 1994).

Biocompatibility and biodegradation of PLA-PGA copolymers and P(L/DL) LA stereocopolymers

Copolymers of PLA and PGA (PLGA) have been used in numerous experimental and clinical applications (Tables 1 and 2). These copolymers offer the capability of altering the degradation rate and mechanical properties of implants by changing the PLA-PGA ratio, which offers the potential to develop site-specific bone fixation and soft tissue-anchoring devices (*Cutright et al.* 1974; *Miller et al.* 1977; *Eppley and Sadove* 1995a; *Eppley and Reilly* 1997). Complete absorption of PLGA 75/25 has been reported in 220 days, PLGA 50/50 in 180 days (*Cutright et al.* 1974), and PLGA 82/18 in 180-450 days (*Eppley and Sadove* 1995a; *Eppley and Reilly* 1997).

With PLGA implants, no implant-related clinical foreign body reactions have been reported. Even biocompatibility in brain tissue has been reported: following implantation of poly (DL-lactide-co-glycolide) (PLG) into the brains of rats, no differences in GFAP reactivity were seen between the polymer-implanted and control sides (injection of the suspension medium into the contralateral hemisphere) at any time point (*Emerich et al.* 1999), and the brain tissue reaction has been shown to be non-specific astrocytic proliferation and a macrophagous-microglial cell reaction, typically found following damage to the central nervous system (*Menei et al.* 1993). The latter group also found that the inflammatory and macrophagous reaction decreased along with biodegradation of the

material and considered the copolymer biocompatible to the brain tissue. PLA-PGA copolymeric Polyglactin 910 (Vicryl®) sutures have been considered better for closure of dural tears than polyglycolide (Dexon®) sutures (*Vallfors et al.* 1981).

P(L/DL)LA (also called PDLLA) is more amorphous and less crystalline and thus degrades faster than pure PLLA (*Kulkarni et al.* 1971). The plates have been shown to degrade more rapidly in subcutaneous tissue than on bone (*Tschakaloff et al.* 1994). SR-P(L/DL)LA plates and screws have been used clinically in orthognatic surgery with a skeletal stability pattern which is comparable to the 'gold standard' of titanium plates and screws (*Haers and Sailer* 1998) (Table 2). No clinical foreign-body reactions caused by P(L/DL)LA devices have been reported.

Biodegradable materials in fixation of craniofacial bones

Biomechanical demands on bioabsorbable plates in fixation of craniofacial bones in children

To be biomechanically safe, bioabsorbable implants should have 1) high initial strength to carry physiological loads during healing, 2) appropriate initial modulus; not too stiff or too flexible for the special purpose where it is used, and 3) controlled strength and modulus retention *in vivo*, in harmony with the increase of strength and modulus of the healing tissue (*Törmälä and Pohjonen* 1995). Of all craniofacial bones, the mandible is prone to the highest biomechanical stresses. Average adult molar bite forces have been recorded to be 726 N, with a maximal force of 4346 N (*Gosain et al.* 1998). Most of these masticatory loads are transmitted to the craniofacial complex through the temporomandibular articulation and maxillary teeth. The occlusal, mainly compressive forces disperse into the midface and neurocranium via trajectories in the zygomatic arch, canine eminence, orbital rims, nasal bones and pterygoid plates (*Shetty and Caputo* 1995). However, most of the neurocranium, especially in infants, is virtually free of masticatory compressive or distractive forces. In growing cranium, the main biomechanical stresses loading areas of osteosynthesis consist of pulsating intracranial pressure, expansive forces caused by the growing brain and cranium, distractive forces caused by scalp closing tensions and wound contraction, and compressive extracranial forces, e.g., the pressure of the child´s head against the contact area. In the literature, biomechanical analyses of neurocranial osteosyntheses are very rare, and they are generally considered "non-loaded". Gosain et al. studied the distractive and compressive forces (parallel to the plate) to failure in plate osteosyntheses in sheep cadaveric cranial bones (*Gosain et al.* 1998). The distractive force of 270 N and compressive force of 200 N broke the non-reinforced, stiff PLGA plate-screw fixation.

In clinical practice, acute forces of relapse are not always negligible, and the fixation system should be initially strong. As a result of the plasticity of infant neurocranium, semi-rigid fixation could possibly be more physiological than rigid fixation, but it should not lead to collapse after remodeling. The fixation system should degrade fast enough to avoid restriction of growth, which may be caused by plates

Tams et al. 1995	3 mongrel dogs, 6 years old	Mandibular fractures	2 mm-thick plates and screws; poly (85L/15D)-lactide with the copolymer poly (50/50)-trimethylenecarbonate-co-epsilon-caprolactone	6, 12, 18 wk	Mechanical properties of the implants were poor, but bone healing was undisturbed without premature failure of the implants. These implants are not safe for complex or comminuted fractures. No FBR, no signs of degradation.
de Roche et al. 1996; *de Roche et al.* 1998	6+6 sheep; 9 sheep (exp. III)	Large orbital defects (diam. 3 cm; connection to sinus frontalis and maxillaris	PDS or P(L/DL)LA 80:20 membranes (0.25 mm) in combination with autogenous bone grafts and fixation with titanium miniplates and screws, or 0.5 mm-thick PLA membrane alone	4 mo; 12 mo (exp. III), results not availab le yet)	After 8 wk, 4/5 reconstructions were separated from sinuses by a mucosal layer. Osteoconductive regeneration along the membrane. FBRs were milder with PLA membranes vs. PDS. PLA implants alone showed the best performance with anatomically complete regeneration.
Ahn et al. 1997	7 Yorkshire pigs	Bilateral tangential osteotomies in frontal bones and infraorbital rims	LactoSorb^{fi} plates and butyl-2-cyanoacrylate adhesive vs. rigid metallic fixation	8 wk	Osteotomies were not performed through the bone! Good consolidation, no displacement. Biomechanical testing (maximum torque to failure): no statist. significant differencies between treatments.
Suuronen et al. 1997	9+9 sheep	Mandibular body osteotomy	SR-PLLA multilayer plates and screws without MMF vs. metallic fixation	24 wk	Uneventful healing.
Bahr et al. 1999	16 sheep	Le Fort I osteotomy	Injection-moulded PLLA/PGA 90:10 plates (2 mm-thick) and 2.7 mm screws, control 2 mm titanium miniplates and screws	16 mo	Torsional weakness of resorbable screws; they had to be melted against the plate. Palpability. Skin abscesses in 2 resorb., 1 tit. at 2 mo. Delayed consolidation (9 mo). Resorbable fixation slightly less stable. Polymeric fragments visible at 16 mo. FBR was not severe.
Kallela et al. 1999c	18 sheep	Mandibular body osteotomies	SR-P(L/DL)LA 70:30 lag screws (9 sheep), stainless steel lag screws (9 sheep), both without MMF	24 wk	All osteotomies consolidated at similar rates. During first 3 weeks, displacements of the fixed fragments were common in both groups. Initial signs of biodegradation were seen. No adverse tissue reactions.

to 10 in 1997 (Table 2). Non-reinforced PLGA implants are mechanically weak and brittle, and can be recommended in paediatric, non-loaded applications. Self-reinforced PLLA and P(L/DL)LA implants have been employed in biomechanically more demanding, loaded conditions, e.g., in orthognatic surgery (*Suuronen et al.* 1994; *Fuente del Campo et al.* 1996; *Haers and Sailer* 1998; *Haers et al.* 1998; *Kallela et al.* 1998). SR-PLGA implants have been used in paediatric craniofacial surgery (*Arnaud, Lauritzen, Marchack and Ninkoviz, personal communication 1999)*.

Table 2. Biodegradable plates and screws used clinically in craniofacial surgery.

Publication	Patients	Implants	Indication	Follow-up	Results
Bos et al. 1987; *Bergsma et al.* 1995	10	As-polymerized, hmwPLLA plates, 2 mm thick	Zygoma fractures	3.3-5.7 years (yr)	>3 yrs: 10 mm thick, swollen area at the site of implantation. Remnants of degraded, crystalline PLLA particles surrounded by a dense fibrous capsule. The implant material slowly degrades into particles with ahigh crystallinity.
Illi et al. 1989; *Illi et al.* 1990; *Illi et al.* 1991	6+4+15 (11 mo - 18 yrs)	PDS bands, PLA headless screws and nuts, without metallic fixation (metallic cerclage in 5 cases)	Stabilization after osteoplastic trepanation and in craniofacial reconstruction	2-20 months (mo)	No complications, "results at least as good as with metallic fixation"; no clinical FBR, infection or cutaneous problems. No material had to be removed.
Ewers and Lieb-Skowron 1990	6 + 5	PDS plate (4-hole)	Orbital fractures (6), extensive frontal bone fractures (5)		Uncomplicated fracture healing in both indications. Delayed FBR in orbita group in 2 pat. in 12 and 14 wk postoperatively, partially absorbed material removed, thereafter no irritation.
Iizuka et al. 1991b	20	PDS plate	Reconstruction of traumatic orbital floor defects	9-45 mo	PDS is suitable for orbital floor reconstruction in defects ≤1-2 cm in diameter. Over-correction seems necessary. The material is well tolerated, is totally absorbed and appears to be replaced by bone in nearly all cases.
Sasserath et al. 1991	? (3 documented)	Biofix^{fi} SR-PGA membrane (0.15 mm or 0.5 mm-thick)	Orbital floor defects and frontal sinus repair	6 mo	Reossification in CT 6 mo postoperatively.
Champy et al. 1992	21 (18-70 yrs)	P(L/D)LA 98:2 plates and screws	18 fractures of the zygomatic bone, 3 maxillary osteotomies	?-3 yr	Biotolerance of the material is very good. The mechanical stability of the assembly is sufficient for the selected indications. Disappointments: the thickness of the plates, difficulty to adapt them to bony surfaces, the fragility of the screws and the slow resorption of the material.
Suuronen et al. 1994	9	Biofix^{fi} SR-PLLA screws (core 2.7 mm)	Bilateral sagittal split osteotomies, no MMF	15-23 mo	No complications, normal primary healing.
Eppley and Sadove 1995b	20 infants	231 LactoSorb^{fi} plates, metallic microscrews	Calvarial osteotomies and repositioning	12 mo	No complications.
Fuente del Campo et al. 1996	32	SR-PLLA plates, metallic miniscrews	Horizontal maxillary osteotomies	12-17 mo	No complications in healing. No FBRs. Unstable fixation in 2 cases (inadequate placement of the screws), all others stable.
Tams et al. 1996	4 cancer patients	as-polymerized PLLA plates, 2 mm® thick, and screws	Mandibular swing osteotomies	1-5.5 yr	Uneventful healing; callus in one patient. After 5.5 yrs nonspecific foreign-body reaction on highly crystalline PLLA remnants.
Habal 1996b	10 (0.5-52 yrs)	Lactosorb¤plates and screws/titanium microscrews	Craniofacial surgery for deformities, trauma (orbit, maxilla), oncological access (orbit, jaw)	?	No loss of fixation stability.
Cordewener et al. 1996	6 (18-67 yrs)	as-polymerized PLLA implants, 0.4 mm-thick	Orbital floor defects	3.5-6.5 yr	2 patients developed enophthalmos because of inadequate positioning or anchorage of the implant. No complications clinically or in MRI.
Tartaro et al. 1996	7	PLLA plates	Mandibular fracture (6), multiple facial fr. (1)	>1 yr	No complications.
Weisberger and Eppley 1997	165	LactoSorb^{fi} plates and screws (metallic microscrews in craniofacial patients)	105 congenital craniofacial deformities, 45 maxillofacial trauma, 10 craniotomy flap fixation, 5 laryngotracheal reconstruction	? 6-24 mo	No adverse tissue reactions, swelling or infection.1 intraoral and 1 intratracheal exposition of the plate without complications. No loss of fixation or bone resorption.
Eppley and Prevel 1997	30	LactoSorb^{fi} 1.5 mm plates, panels and screws LactoSorb^{fi} 2.0 mm plates and screws	Fractures of the upper and midfacial skeletal regions	6-12 mo	1 yr (17 pat.): No infection, erythema of the overlying skin, fracture instability or relapse, or osteolysis radiographically. 6 mo (11 periorbital cases): no longer palpability, radigr. healing
Eppley 1998	11	LactoSorb^{fi} plates (35) and screws (151)	Le Fort I (isolated fractures)	0-1 yr	Provided good bone (non-comminuted) was available for fixation placement, no differences were observed in intraoperative maxillary stability or long-term postoperative results.
Kallela et al. 1998	25	Bionx^{fi} SR-PLLA screws	Mandibular advancement without MMF	1 yr	SR-PLLA screws are considered to be comparable to other forms of rigid internal fixation for fixation of bilateral splitting osteotomies after mandibular advancement, as far as skeletal stability is concerned.

Haers and Sailer 1998	10	SR-P(L/DL)-LA (70:30) plates and screws	Bimaxillary surgery and genioplasty without postoperative rigid intermaxillary fixation	6 wk	All jaws were clinically stable and there was no clinical evidence of foreign body reactions. None of the plates, which were bent at room temperature, broke. The screw heads broke or had an insufficient fit in the bone in 12 of 305 (3.9%) screws. The short-term skeletal stability pattern is comparable to the 'gold standard' of titanium plates and screws.
Bouwman and Tuinzing 1999	4 (24-31 yrs)	SR-PGA 1.5 mm rods (2 pat.), SR-PLLA 2 mm screws (2 pat.)	Retrognathia: bilateral sagittal split osteotomies of the mandibular ramus for advancement	1-6 yr	Uneventful healing. Technical difficulties in inserting the rods; therefore rods were not recommended and screws preferred.
Kallela et al. 1999a	11 (25-51 yrs)	SR-PLLA lag screws	Anterior mandibular fractures; MMF was used to treat concomitant mandibular condyle fractures for 2 weeks in four patients and for 1 and 5 weeks in two patients.	6-12 mo	Healing of all anterior fractures was uneventful, with no displacement or delay of bony union. No adverse reactions to the biodegradable screws were seen.
Kallela et al. 1999b	47 (17-54 yrs)	SR-PLLA screws (core 2.5 mm, thread 3.5 mm)	Mandibular bilateral sagittal split osteotomy	0.5-5 yr	Clinical recovery and radiological osteotomy healing were uneventful. Majority of the screw channels remained radiolucent.
Edwards et al. 1999	37	PLLA-PGA screws (2.5 mm, 13-15 mm), 3 screws on each side, no MMF	Mandibular bilateral sagittal ramus osteotomies (setback or advancement)	3-17 mo	No problems in immediate postoperative stability or relapse. Screw holes radiolucent after 1 yr.
Suuronen et al. 1999	>200	SR-PLLA screws; SR-P(L/DL)LA plates and screws (1.5-2.8 mm); SR-PGA/PLA in paediatric patients	Trauma, orthognatic, craniofacial, access osteotomies, cancer surgery. Costochondral grafts in arthroplasties (ankylosis)	since 1991	Results comparable to the use of similar metallic devices. Very low complication rate. Stability comparable to metallic fixation. Devices also recommendable in cancer surgery (CT, MRI and postoperative radiotherapy).

Properties of an ideal implant for craniofacial surgery

Qualities that an ideal fixation system must possess include adequate strength and rigidity, lack of adverse reactions (i.e., not toxic, allergenic, immunogenic, mutagenic, or teratogenic), lack of interference with bone healing, lack of intracranial migration, lack of visibility and palpability, and avoidance of an implant removal operation. Surgeons appreciate good handling properties, such as malleability of plates in room temperature and good torsional strenght of screws.

The ideal implant would be made of a bioabsorbable material, which (1) can be fabricated and designed with appropriate initial strength to meet the biomechanical demands, (2) degrades in a predictable fashion and retains the desired integrity and strength to provide biomechanical stabilization to the healing bone for the required time, (3) causes no deleterious tissue responses necessitating device removal or other surgical intervention, and (4) disappears completely.

THE PRESENT STUDY

Aims of the study

The study was aimed at answering the following questions:

What is the nature of the basic consolidation process of a craniotomy line, when plated with a titanium plate and an SR-PLLA plate?
What is the biocompatibility of these implants, and what is the biodegradation rate of an SR-PLLA plate?
(Paper I)

Radiographic assessment of these two kinds of plated craniotomy lines: is there any difference in assessing the consolidation process of the lines?
(Paper II)

What is the biocompatibility of and tissue reactions to an SR-PLLA plate in an intraosseous environment in sheep cranial membranous bone?
(Paper III)

Can a non-reinforced, flexible, membrane-like PLA96 plate be used for fixation of unstable craniotomies in lambs?
What is its biocompatibility, effect on the consolidation process, and rate of bioabsorption?
(Papers IV and V)

Can SR-PLLA and SR-PGA miniscrews be used for plate fixation of lamb cranial bones?
What is their biocompatibility and rate of bioabsorption in lamb neurocranium?
(Papers IV and V)

MATERIALS AND METHODS

This experimental study was approved by The Research Animal Commission of the Faculty of Veterinary Medicine, University of Helsinki, and by The Provincial Administrative Board, according to Finnish law.

Experimental animals

Skeletally immature sheep were chosen as the experimental animals, since the size, thickness and growth pattern of the membranous bones of the sheep skull are more comparable to those of the young, growing human skull than those of small mammals. The Finnish Landrace sheep used in the present study grow slowly and may gain weight up to 80 kg. All sheep were clinically healthy and conditioned at least two weeks before surgery. In the first experiment (I, II), 15 female sheep, 16-20 months old, weighing 37-57 kg (mean 45 kg) were operated upon. In the second experiment (III), 6 sheep (5 female, 1 male), 8-10 months old, weighing 31 to 45 kg (mean 38 kg) were operated upon; and in the third experiment (IV,V), 20 female, 4-7-month-old sheep, weighing 22-32 kg (mean 25.6 kg) were operated upon.

Implants

The SR-PLLA plates (I, II, III) were manufactured in the Biomaterials laboratory, Tampere University of Technology, Finland, using a self-reinforcing technique involving fibre orientation. Purified medical grade PLLA raw polymer with a viscosity average molecular weight (Mv) of 675 000 g/mol was used. After melt-state and subsequent hot solid-state processing, the Mv decreased to 220 000 $\pm$ 20 000. Steriliza-

Table 3. Experimental animals and follow-up times.

Study	n	Follow-up time (weeks)						
		4	6	12	20	26	52	104
Craniotomy lines (I,II)	15		4	4	4		2	1
Intraosseous plating (III)	6			2	2			2
Frontal craniotomies (IV,V)								
SR-PGA miniscrews	10	2	2	2		2	1	1
SR-PLLA miniscrews	10*		2	2		2	2	1

*One sheep left for long-time follow-up.

tion by gamma irradiation with a minimum dose of 25 kGy further decreased the Mv to 50 000 ± 5 000. The percentage crystallinity of the implants was 50 ± 5 % as determined by DSC measurements. The plates were punched, the 1.5 mm holes being at the apices of an equilateral triangle, the side of which was 3 mm. The plexiglass-like plates were 0.5 mm thick, 12 mm wide, and originally 30 mm long but were shortened with scissors to the desired length at operation. Titanium miniscrews were used for fixation of the SR-PLLA plates (I, II).

The P(L/D)LA (96/4) plates (PLA96) and SR-PLLA and SR-PGA miniscrews (IV,V) were manufactured at Tampere University of Technology, Tampere, Finland. The stereocopolymeric plates (research samples) were non-reinforced and non-oriented, and composed of 96% L- and 4% D-lactide, processed by compression moulding and gamma-sterilized (2.5 Mrad). The 0.4 mm-thick, transparent, flexible, punched sheets were cut with scissors to 20 x 30 mm at operation. The SR-PLLA and SR-PGA miniscrews were processed by compression molding (diameter 2 mm, core 1.5 mm, length 5-8 mm, Biofix®, Tampere, Finland) and equipped with cross heads. A special tapping instrument for these screws was used. When necessary, long screws were shortened with a thin oscillating saw or a hot wire loop.

The 4-hole titanium miniplates (0,6x4x25 mm, OsteoFix Inc., Oulu, Finland) were fixed with 3 mm- and 5 mm-long self-tapping titanium miniscrews (diameter 2 mm, core 1.5 mm, OsteoFix Inc., Oulu, Finland), four screws in one plate (I, II, IV, V).

Preoperative procedure, anaesthesia and postoperative care

Food was withheld for two days preoperatively. Water was supplied *ad libitum*. Medetomidine at 20 microg per kg bwt was given intravenously (iv). Anaesthesia was induced iv by using propofol at 3 mg per kg bwt and maintained with 2-2.5 % halothane. The sheep were intubated and positioned in sternal recumbency with the head extended and fixed on a cushion. During the operation, 1000 ml of iv fluid (Ringersteril®, Medipolar, Oulu, Finland), metronidazole at 11 mg/kg iv, and benzylpenicillin sodium at 35 000 IU/kg iv were administered. Methylcellulose eyedrops (Oftan-MC®, Leiras, Finland) were used to avoid ocular drying and irritation. The entire head was shaved, washed, and sterilized with chlorhexidine gluconate. 10-20 ml lidocain cum adrenalin (Lidocain 10 mg/ml c. adrenalin®, Medipolar, Oulu, Finland) was injected subcutaneously in the operative area. Before the animals recovered (in the third experiment), Flunixin (Finadyne® 50 mg/ml, Orion, Espoo, Finland), 2.2 mg/kg, was administered.

Postoperatively, the sheep were returned to their pens and fed *ad libitum*. Benzylpenicillinprocaine (Ethacilin vet injekt® 300 000 IU/ml, Intervet, Boxmeer, Holland), 35 000 IU/kg sc as infection prophylaxis, and phenylbutazone (Reumuzol® vet injekt 200 mg/ml, Lääkefarmos, Turku, Finland), 8 mg/kg iv as an analgesic were administered once a day for three days. Before euthanasia the sheep were stunned with electricity.

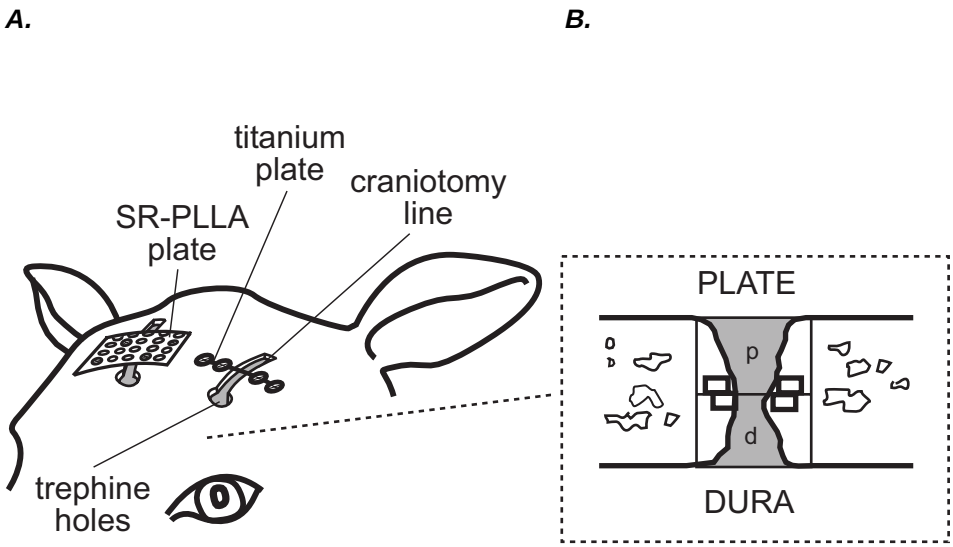


Figure 3. The first experiment: craniotomy lines (I,II): the experimental design (A) and histological sections and fields of histomorphometric analysis (B).

Operative techniques

In all operations, the calvarium was exposed through a sagittal 8-10 cm-long incision in the midline, and the dissection was performed in subperiosteal plane, with periosteum attached to subcutaneal layers. Thermal damage was avoided by using continuously flowing saline solution during bone preparation. In the end of the procedure, periosteum was carefully repositioned and sutured in the midline with resorbable 3-0 Vicryl®-sutures (Ethicon, Norderstedt, Germany). The wound was closed in layers using 4-0 Vicryl® insubcutaneous tissue and non-resorbable 3-0 Suturamid® in the skin (Ethicon).

Craniotomy lines plated with SR-PLLA and titanium miniplates (Papers I and II)

Two sawing lines were marked on the bone symmetrically on both sides of the round, thickened area located centrally on the sheep skull, starting 15 mm laterally from the midline and heading posterolaterally at a 10° angle (Fig. 3A) from the sagittal suture. AO mini-air-drill instrumentation was used. A 5.0 mm-diameter round burr was used to make two anterior holes through which the dura was detached from the bone with a spatula. A Lindemann reamer (2.3 mm) and a skull guard were used to saw transosseous osteotomy lines, 2.3 - 2.5 mm wide and 22-24 mm long, carefully protecting the dura. On the right side, an SR-PLLA plate was set and fixed with four 3 mm or 5 mm self-tapping titanium miniscrews, using the holes in the plate (Fig. 3A). Over the left osteotomy line, a 4-hole titanium miniplate was set correspondingly.

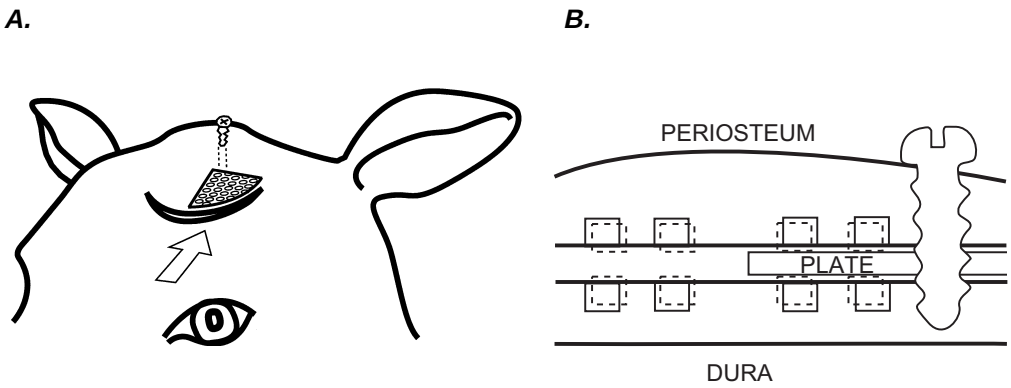


Figure 4. The second experiment: intraosseal plating (III): the experimental design (A) and histological sections and fields of histomorphometric analysis (B).

Intraosseous implantation of SR-PLLA plates with SR-PLLA miniscrew fixation (Paper III)

An AO mini-air saw was used to make a narrow horizontal slit in the anterior half of the round, thickened area located centrally on the sheep skull (Fig. 4A). An SR-PLLA plate was inserted into the osseous slit on the left side of the sagittal suture and fixed with an SR-PLLA mini-screw. The screw channel was drilled with a depth stopper to 6 mm, and tapped. The non-plated right side of the osseous defect was left as it was to serve as a control.

Cranial osteotomies fixed with PLA96 plates and SR-PLLA or SR-PGA miniscrews versus titanium miniplating (Papers IV and V)

A paediatric cranial perforator and craniotome (Heifetz skull trepan 6/9 mm, GB 340, and paediatric craniotome, Freiburg pattern, GB 292, Aesculap®, Germany) were used for preparation of two symmetrical, rectangular (15 x 18 mm) osteotomies in the frontal bone (Fig. 5A). The dura was detached from the bone with a spatula, and thermal damage was avoided by using continuously flowing saline solution during bone preparation. The bone piece was repositioned without contact to the surrounding bone, and fixed on the right side with a 4-hole titanium plate and miniscrews. On left side, a PLA96 plate (covering both the bone segment and the trephine holes) and four SR-PLLA miniscrews (ten sheep) or four SR-PGA miniscrews (ten sheep) were used for fixation. The screws were placed in consecutive order; two screws in the refixed bone segment and one screw in each end. Shaping of the resorbable plate was unnecessary because of the flatness of the calvarium and pliability of the plate. After fixation, minimal inward movement of the bone segment on the resorbable side could be brought about by firm finger compression, but because of the flexibility of the plate, it immediately returned to its original position.

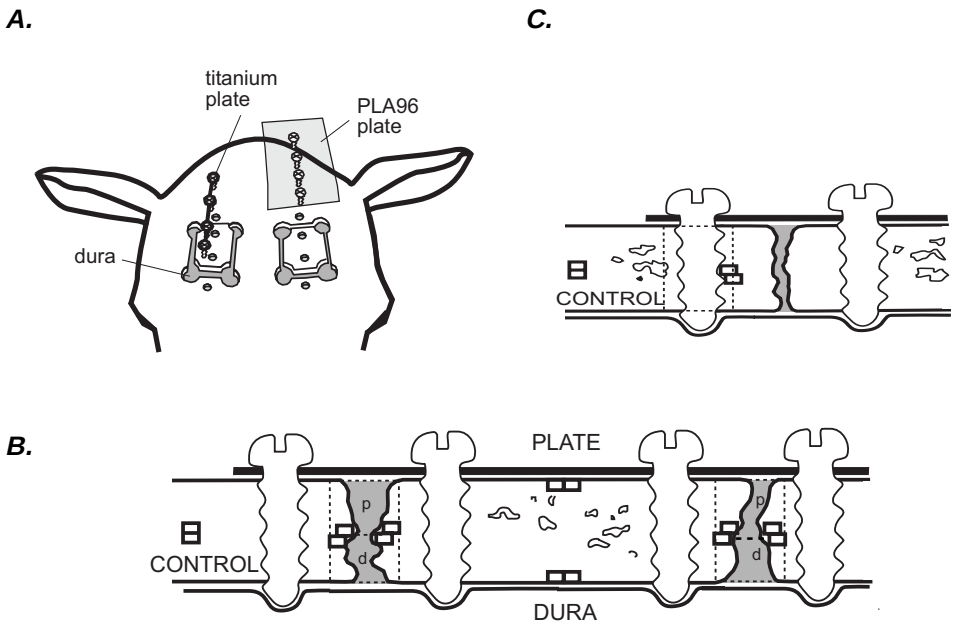


Figure 5. The third experiment: unstable craniotomies (IV,V): the experimental design **(A)**, and histological sections and fields of histomorphometric analyses on consolidation **(B)** and miniscrews **(C)**.

Follow-up

In the first experiment (papers I and II), the sheep were sacrificed at 6, 12, 20, 52 and 104 weeks postoperatively in groups of 4, 4, 4, 2 and 1, correspondingly (Table 3). Of these 15 sheep, 6 sheep were used in strength studies (non-published) at 6, 12 and 20 weeks. In the second experiment (paper III), the sheep were sacrificed at 6, 20 and 52 weeks postoperatively, in groups of two. In the third experiment (papers IV and V), the sheep were grouped according to the nature of the biodegradable screws and sacrificed at 4 (2 PGA), 6, 12, 26 (2 PGA, 2 PLLA), 52 (1 PGA, 2 PLLA) and 104 (1 PGA, 1 PLLA) weeks. One sheep (PLLA) was left for long term follow-up.

Examination methods

Macroscopic observation (I-V)

Postoperatively, the sheep were observed as regards neurological symptoms, movement and appetite. The operated areas were observed as regards infection and swelling. After sacrifice, during dissection, attention was paid to wound and osteotomy healing, swelling, seromas, appearance of the devices on the bone and, after cutting the specimens, the possible appearance of plates and screw tips on the dural side and on the brain. Most of the operated areas were photographed during dissection.

Experiment	n (sheep)	Histology	OTC-fluorescence	Histomorphom.	Micro-radiography	Radio-graphy	CT	MRI	Tensile strength
Craniotomy lines (I)	9	9	9	9					
Craniotomy lines (non-publ.)	6								6
Craniotomy lines (II)	9				9	9	9		
Intraosseous plating (III)	6	6		6					
Unstable craniotomies (IV,V)									
SR-PGA miniscrews	10	10		10		10		10	
SR-PLLA miniscrews	10*	9		9		1**		1**	

*One sheep left for long-term follow-up.
**104-week follow-up

Table 4. Experiments and the examination methods.

Histology (I-V)

The operated areas were dissected free of skin and cut away from the skull with an oscillating saw. The titanium material was removed. The specimens were fixed in a series of ethanol solutions of rising concentration (70-99%) and embedded in methylmethacrylate. Five-micrometer-thick sections were cut in the middle of the plated area, perpendicular to the osteotomy line (I-III) (Figs. 3B and 4B), or through the screw line (IV,V) (Fig. 5B), with a Reichert-Jung microtome (Nussloch, Germany) and stained by using modified Masson-Goldner trichrome (*Goldner* 1938) and haematoxylin-eosin methods. Polarizing microscopy was used to identify birefringent polymeric material in the specimens. The presence of inflammatory cells within the sample fields was assessed qualitatively, using a magnification of 400 x for cell identification. The findings were checked by an experienced pathologist.

Microradiography and OTC-fluorescence (I, II)

In the first experiment (I, II), oxytetracycline hydrocloride (5 mg/kg iv), was injected 13 and 9 days before the end of the follow-up time to mark newly-formed bone in tetracycline-labelling studies (*Milch et al.* 1958). For tetracycline fluorescence and contact microradiography studies, 80-micrometer-thick sections were cut with a Leitz Saw Microtome 1600 (Wetzlar, Germany). For contact microradiography (Faxitron X-ray system, Model 43855 A, Hewlett Packard), IMTEC film was used (High Resolution Plates, Ultra flat, Type 1A, Sunnyvale, California, USA), and the technical values were 21 kV, 3 mA, with a 15 min exposure time and 0 cm film-focus distance. Fluorescence microscopy was performed using an HBO 220 ultraviolet lamp (Osram, Berlin, Germany) and a Leitz BG 812/6 primary filter (Wetzlar, Germany). As the quality of the histological sections was excellent, these methods did not add a great deal of further information and were used only in the first experiment.

Histomorphometry (I, III- V)

In each study (I,III-V), all histological specimens were quantitatively analyzed for different parameters histomorphometrically (*Revell* 1983). A Leitz Diaplan microscope (Leitz, Wetzlar, Germany) was linked via a television video camera to a semiautomatic imaging analysis system (Kontron MOP Videoplan, Munich, Germany). The microscopic field was shown on a visual display unit. Measurements of surface areas on the screen were carried out manually by using a digitizer and a cursor. The technique was practised by repeating series of measurements until the results were reproducible.

In the first experiment (I), two standardized sample fields of 4.01 x 2.39 mm were delineated above and below the midline of the osteotomy to the overall pericranial and endocranial levels, thus reflecting the plated (p) and dural (d) sides of the osteotomy, correspondingly (Fig. 3B). The size of the non-ossified area (remaining bone defect) and the trabecular bone fraction of the whole tissue area on each side were measured. Within the sample fields, the marginal zone of the proliferating bone in the middle of the osteotomy (Fig. 3B) was systematically examined (using a magnification x 100) as regards the total trabecular bone volume fraction (including calcified trabeculae and osteoid), the total osteoid surface fraction (of the trabecular bone surface), and the active osteoid formation surface fraction (osteoid surface covered by active osteoblasts). Four sample fields were analyzed in each specimen. Ongoing calcification of osteoid was confirmed by fluorescence microscopy.

In the second experiment (III), connective tissue initially filled the created bone defect. Replacement of the connective tissue by bone tissue and formation of osteoid were measured on both the plated and the control sides. Four sample fields of 0.37 x 0.61 mm (magnification x 100) were delineated in the host tissue - implant interface to measure the percentage of connective tissue in the total tissue volume (Fig. 4B). Another four fields were delineated in the bone adjacent to the connective tissue capsule, and a corresponding number of fields on the contralateral side to measure the total trabecular bone volume fraction, including calcified trabeculae and osteoid, the total osteoid surface fraction, and the active osteoid formation surface fraction.

In the third experiment (IV,V), principally the same protocol was used as in the first experiment. The non-consolidated bone defect areas (IV) were measured in windows corresponding to the original bone defect (original width 2.35 mm, window width 2.39 mm), using a magnification of x 16 (Fig. 5B). The percentage of remaining defect was taken to be the mean value of the plate (p) sides and dural (d) sides. New bone formation was analyzed in detail using a magnification of x 100 in ten standardized windows (0.37 x 0.61 mm) (Fig. 5B). The areas of interest were the consolidating bone defect (four fields; the more poorly consolidated line was selected), the plate/periosteal and dural sides of the fixed bone segment (two fields each, measurements in the intact dural area) and the control area (two fields). The control area was selected in the same specimen in intact bone in the same sagittal plane where the periosteum had been elevated.

Resorption of the polymeric material in the screw channels and the effect of the polymer on formation of new bone around the channel were also analyzed (V) (Fig. 5C).

The screw channels were analyzed at a magnification of x 16, and 2.39 mm-wide sample fields were delineated inside the bone tissue with the screw channel in the middle. Because cutting the specimens exactly in the middle of all the screws or screw channels was technically impossible, only the screws cut in the middle or channels of maximum width were included in the analysis. The percentage of tissue other than bone (including connective tissue and polymeric material in the screw channel) and the percentage of polymeric material in the total tissue volume were measured. Two smaller fields (0.37 x 0.61 mm) beside the screw in the middle of the bone and outside the osteotomized segment in intact bone in the same section (control), were analyzed for total trabecular bone volume fraction and osteoid surface fraction, using a magnification of x 100.

Radiography (II, IV, V)

In the first experiment (II), after sacrifice, the osteotomies in each skull were examined by using tangential plain films (settings of 57 kV and 32 mAs and 120 cm focus-object). The radiographs were evaluated as regards visibility of the osteotomy and osteosynthesis devices, new bone formation, osteolysis, and union of the osteotomy.

In the third experiment (IV, V), the specimens containing SR-PGA screws and the two-year follow-up sheep with SR-PLLA screws, with their contralateral titanium-fixed counterparts, were investigated by plain film radiography. Osteotomized calvarial areas were dissected free of soft tissue and removed with an oscillating saw. The bone specimens were examined in anteroposterior (AP) and tangential directions (settings of 48 kV, 25-32 mAs and 42-44 kV, 25 mAs, and 100 cm focus-object). The AP images were analyzed as follows: The four trepanation holes were measured in two perpendicular directions. The result was expressed as the mean diameter of the four holes (IV). The minis-crew holes were measured for their greatest diameter (V). The length of the visible osteotomy line was measured and expressed as a percentage of the length of the original osteotomy line (IV). All measurements were performed by a radiologist using a magnifying lens (x7, with a precision scale of 0.1 mm).

Computerized tomography (II)

In the first experiment (II), after sacrifice, the skulls were examined by CT. Contiguous 3 mm-thick coronal slices were taken from the skulls of the first 6 sheep with a scanner (Philips, Tomoscan 60/TX, Tokyo, Japan). A field of view (FOV) of 25 cm, a window of 2200-2500 Houndsfield Units (HU) and a level of 250-300 HU were used. The 2 last sheep, at the time of 52 weeks« follow-up, were examined by spiral CT (GE HiSpeed Advantage, Milwaukee, Wisconsin, U.S.A.). The 3 mm-thick slices were imaged in the coronal plane. An FOV of 12.5 cm, a window of 2200 HU and a level of 600 HU were used. Blurring of the edges of the osteotomy line, new bone formation and bone bridges were regarded as radiographic signs of healing of the osteotomy. The integrity of the screws and plates was analyzed, and any migration or breakage of the material was noted.

Magnetic resonance imaging (IV)

In the third experiment (IV,V), the skulls containing SR-PGA screws and the two-year follow-up sheep with SR-PLLA screws were investigated by magnetic resonance imaging (MRI) and plain film radiography, because PGA implants in particular and PLLA implants in the long term may be associated with osteolytic reactions and foreign-body reactions. MRI was performed using a 0.1 T resistive unit (Merit, Picker Nordstar Co., Helsinki) and a head coil. A scout image in a coronal direction was used to locate the craniotomy areas. Regions of the craniotomies were imaged in contiguous oblique slices. The examination included a T1-weighted pulse sequence (PS3D 125/20) with a flip angle of 80 degrees and a T2-weighted pulse sequence (PS 100-40) with a flip angle of 90 degrees. The image acquisition time was 5 min 24 s for the T1 images and 7 min 12 s for the T2 images. The slice thicknesses were 3 mm and 5 mm respectively, and the matrix ,144 x 256.

Mechanical testing procedure (unpublished)

The operated areas were carefully dissected and removed with an oscillating saw along the border of the SR-PLLA plate, and a corresponding area on the titanium plated side. In 6-week specimens the SR-PLLA plate was removed; in other specimens the SR-PLLA plate could not be removed. All titanium material was removed before testing. The specimens were kept in saline solution until mechanical testing was carried out (within 24 hours). Testing was performed at 20°C with a J.J. Lloyd testing machine (J.J. Lloyd Instruments, Southampton, England) at a testing speed 10 mm/min.

Tensile strength was measured along the long axis (Fig. 6). The specimens were attached at both ends, and the free testing length was 10 mm. Tensile strength was calculated by using a formula:
strength = F / A [MPa]

Statistical methods

The numerical data obtained in histomorphometry allowed the results to be evaluated by statistical methods (I, IV,V). In the first experiment (I), paired t-tests with one tailed interpretation and two-way analysis of variance were used. In the third experiment (IV,V), repeated analyses of variance and two-way analysis of variance were used. P values less than 0.05 were considered statistically significant. The statistical analysis was performed by a statistical expert.

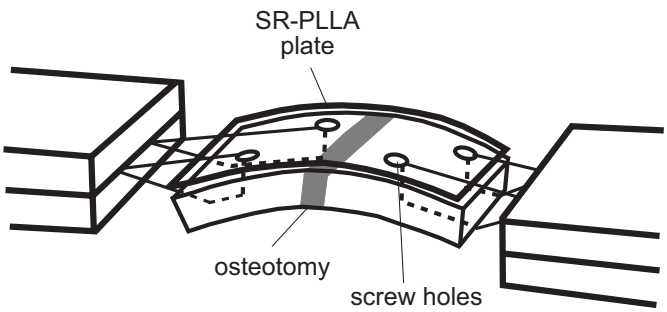


Figure 6.
Tensile strength testing arrangements. The piece of bone with craniotomy in the middle was fixed by metallic threads going through the screw holes (screws removed).

RESULTS

Consolidation of craniotomy lines plated with SR-PLLA and titanium miniplates (I,II)

MACROSCOPIC: All sheep recovered uneventfully without wound infections or signs of foreign body reactions. At 52 weeks the polylactide plate had softened, and at 104 weeks, it had disappeared.

Consolidation: From an original width of 2.3-2.5 mm, the osseous defects had narrowed to 1-2 mm by 6 weeks, and were filled with dense connective tissue (Figure 7A,B and 8). Osseous bridging over the osteotomy line occurred by 12-20 weeks in the SR-PLLA specimens (C,E), whereas a 0.3-0.5 mm (D) or 0,5-1 mm (F) wide, connective tissue filled gap was detected on titanium sides. SR-PLLA-plated lines showed very dense and even ossification, whereas in the titanium plated lines the bone edges were “clumped“ and rounded. At 52 weeks, fibrous union was obvious on both titanium sides (H). At 104 weeks both osteotomies showed complete healing, and the bone was lamellar and dense.

BIODEGRADATION: Throughout the study, the SR-PLLA plates were surrounded by a thin, dense connective tissue capsule that also filled the holes of the plates (Figure 7). At 6 weeks (A), some macrophages could be seen in the vicinity of the SR-PLLA plates. At 12-20 weeks (C,E), microscopical swelling and cracking of the plate could be observed. At 52 weeks, fragmentation of the SR-PLLA plate occurred parallel to the fibrils of the material. The amount of macrophages had increased, and some giant cells could be seen in the deep cracks between the fibrils. At 104 weeks (I), in the area where the SR-PLLA plate had been, tiny fragments of the polymer were found, which were being actively absorbed by macrophages and a few giant cells (J). No signs of an inflammatory process could be seen. The connective tissue layer had thickened microscopically. A new, thin bony layer had appeared in the area of the former SR-PLLA plate (arrows in I).

OSTEOID FORMATION AND OTC-FLUORESCENCE: In the regenerating border of the bone defect the osteoid surface fraction (OSF) was greatest at six weeks (Figure 9), being 63 % on the SR-PLLA side, and 40 % of the trabecular bone surface was covered by active osteoblasts. At 12 weeks, the OSF and fraction of active osteoblasts were still high on the polylactide side. The titanium specimens showed slower healing and considerably less OSF than the SR-PLLA plate specimens. As a result of complete consolidation, the OSF had diminished on the SR-PLLA-plated side at 20 weeks, whereas it was higher on the non-consolidated, titanium sides. At 52 weeks, osteoid formation had finished in all samples, including

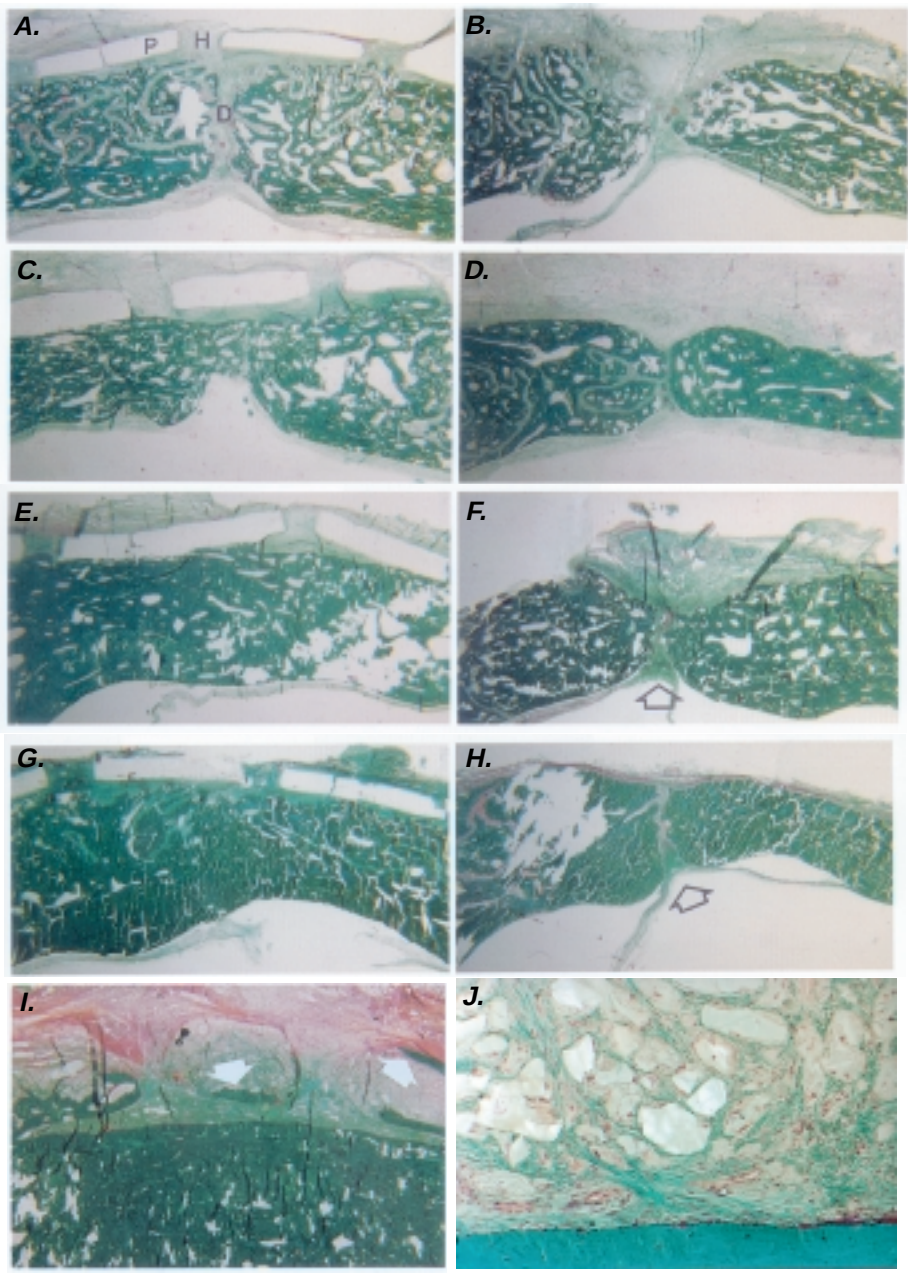


Figure 7. Photomicrographs of sheep calvarial osteotomy lines 6 weeks (A,B), 12 weeks (C,D), 20 weeks (E,F), 52 weeks (G,H) and 104 weeks (I,J) postoperatively. SR-PLLA-plated side in A,C,E,G,I,J, and titanium-plated side in B,D,F,H. The SR-PLLA plate is marked with "P" in figure A, and the hole of the plate with "H", and the remaining bone defect with "D". Note consolidation under the SR PLLA plate at 12 weeks (C) and incomplete consolidation under the titanium plate at 20 weeks (F) and 52 weeks (H) (arrows). Cracking of the SR-PLLA plate starts at 20 weeks (E), and advanced degradation is seen at 104 weeks (I), where thin layers of new bone (arrows) can be detected around the former plate, and macrophages around the polylactide particles (J). Masson-Goldner trichrome, original magnification x 12.5(A-H), x 25(I), and x 400(J). Reproduced by kind permission of *Plastic and Reconstructive Surgery*, from 101 (1998) 123-133.

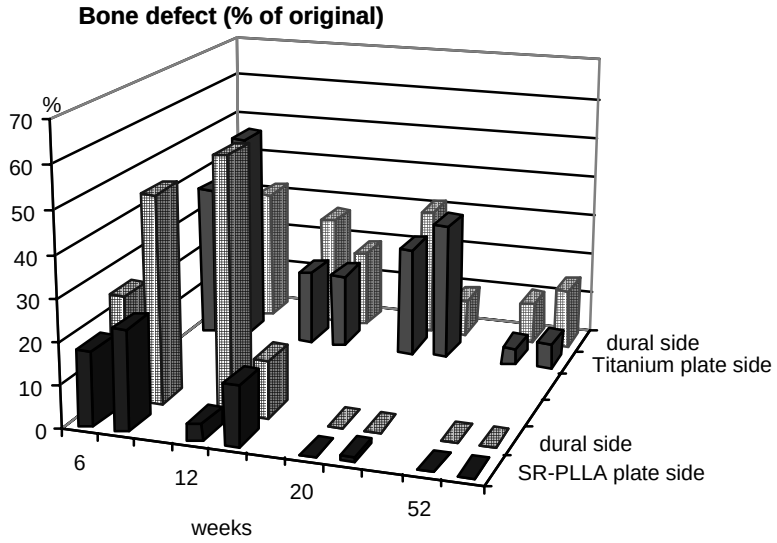


Figure 8. Histomorphometric analysis of the consolidation process: remaining bone defect area: The defect healed significantly faster on the SR-PLLA side ($p<0.05$) than on the titanium side. Consolidation beneath the plates (Field p in Fig. 3B) was significantly more effective on the SR-PLLA plate side than on the titanium plate side ($p<0.001$). The difference on the dural sides between the SR-PLLA specimens and the titanium specimens (Field d in Fig. 3B) was not significant. "Clumping" and rounding of the bone edges on titanium sides caused variability in the histomorphometric measurements.

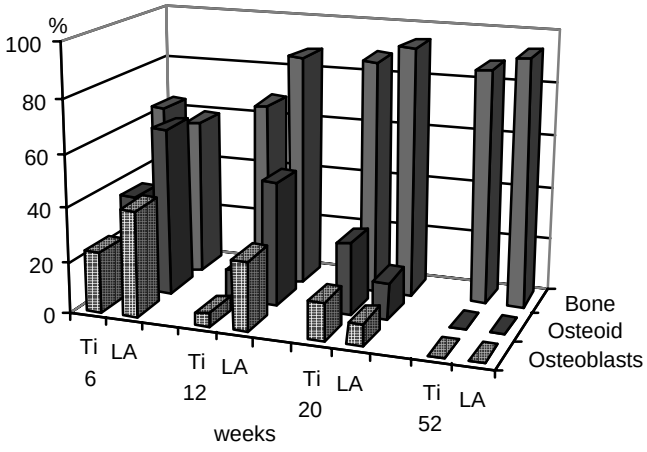


Figure 9. Histomorphometric analysis of regenerating bone margins in SR-PLLA-plated (LA) and titanium-plated (Ti) sheep craniotomy lines: bone (the total trabecular bone volume fraction of the total bone volume, including calcified trabeculae and osteoid), osteoid (the total osteoid surface fraction of the total trabecular bone surface), and osteoblasts (the active osteoid formation surface fraction of the total osteoid surface, e.g. osteoid surface covered by active osteoblasts).

the titanium sides that had not consolidated completely. OTC-fluorescence confirmed these findings, as abundant two-layer fluorescence was observed in the osteoid formation areas, and OTC-fluorescence was not apparent at 52 weeks.

PLAIN FILM RADIOGRAPHY showed false positive union of the titanium-plated osteotomy in three cases and was thus not reliable in imaging ossification. This was due to the fact that the direction of the central X-ray of the beam was not parallel to the osteotomy line. This subsequently resulted in overlapping of the edges of the narrow false union of the osteotomy. The SR-PLLA plate was radiolucent, and no signs of a foreign body reaction or osteolysis around the biodegradable plate were noted. Loosening of the titanium plate and screws was noted in one sheep at 52 weeks.

COMPUTERIZED TOMOGRAPHY: The findings obtained from CT correlated well with findings in histology and microradiography. Signs of osseous bridging on the SR-PLLA-plated side were visible 12 weeks postoperatively, and complete consolidaosteotomy line and was interpreted as tion was seen at 20 weeks. On the titanium side, CT revealed osseous defects and rounding of the bone edges in consecutive cases. However, adjacent to the titanium plate, scatter impeded evaluation of a very narrow non-union, whereas the presence of the SR-PLLA plate did not result in any

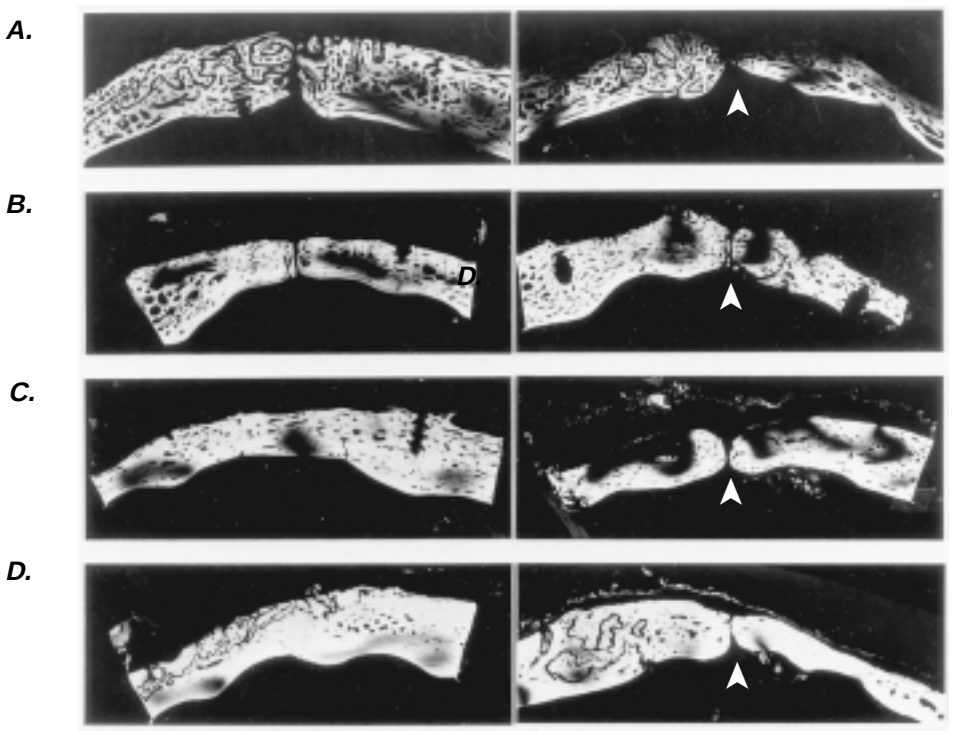


Figure 10. Microradiography: SR-PLLA-plated specimens on the left, titanium-plated specimens on the right, 6 weeks (A), 12 weeks (B), 20 weeks (C) and 52 weeks (D) postoperatively. An osseous defect is visible in all titanium-plated specimens (arrows). The SR-PLLA-plated craniotomies appeared to consolidate by primary union, whereas clumpy bony masses were evident on the bone margins on the titanium sides. Reproduced by kind permission of *Journal of Craniofacial Surgery* from 8 (1997) 446-451.

artefacts in CT. No adverse tissue reactions to the resorbable material were seen in CT, but a loosened titanium plate and screws caused a soft tissue prominence in a sheep at 52 weeks.

MECHANICAL TESTING OF CRANIOTOMY LINE SPECIMENS: Densely punched SR-PLLA plates were very difficult to remove, as connective tissue had grown through the holes. During dissection, they fragmented, and tensile (distraction) strength testing of the plates could not be performed. From 12 weeks on, the plates were macroscopically fractured between the holes. They were impossible to remove and were left *in situ*. In 5 of 6 sheep, the SR-PLLA-plated craniotomy line was stronger than the titanium-plated line (Table 5, Figure 11.).

Follow-up	Specimen	Thickness (mm)	Maximal force (N)
Control	Piece of intact cranial bone (at the time of operation)	4.4	**181.60**
6 weeks	SR-PLLA side	2.6	**30.29**
	Titanium side	3.7	**19.99**
	SR-PLLA side	4.5	**15.18**
	Titanium side	4.0	**21.90**
12 weeks	SR-PLLA side	4.0	**85.75**
	Titanium side	4.8	**67.98**
	SR-PLLA side	4.5	**99.72**
	Titanium side	4.4	**57.76**
20 weeks	SR-PLLA side	3.5	**93.92**
	Titanium side	5.1	**48.75**
	SR-PLLA side	6.7	**421.1**
	Titanium side	6.9	**364.3**

Table 5. Maximal force (N) needed to break the craniotomy lines.

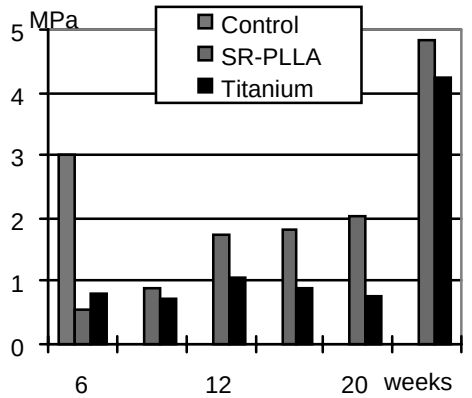


Figure 11. Tensile strength (MPa) of the craniotomy lines. The SR-PLLA plates were left *in situ* in 12- and 20-week specimens.

Intraosseal implantation of SR-PLLA plates with SR-PLLA miniscrew fixation (III)

MACROSCOPIC: There were no clinical foreign body reactions. The outlines of the screw heads were sharp and hard on palpation for 20 weeks. At 52 weeks, the screw heads had partially lost their original shape, but no signs of inflammatory soft tissue reactions were present.

CONSOLIDATION AND OSTEOID FORMATION: By 6 weeks, the osseous defect on the non-plated side had consolidated. Histomorphometric analysis showed no difference in the average amount of bone tissue, the osteoid surface fraction, or the amount of active osteoblasts between sample fields on the plated and non-plated areas during the follow-up time of one year (Fig. 12). At 52 weeks, the bone was smooth, even and very dense on both the plated and control sides. The amount of osteoid and the number of osteoblasts had diminished compared with the 20-week specimens. No signs of osteolytic reactions were seen.

BIODEGRADATION: The SR-PLLA plates and screws incorporated well and were surrounded by a thin, dense connective tissue capsule that also filled the holes of the plates. This capsule gradually thinned, and at 20 weeks the holes of the plate were filling with bony trabeculae (Fig. 13), and bone tissue could also be seen in the narrow area between the plate and the core of the screw. At 52 weeks, the intraosseal parts of the implants were

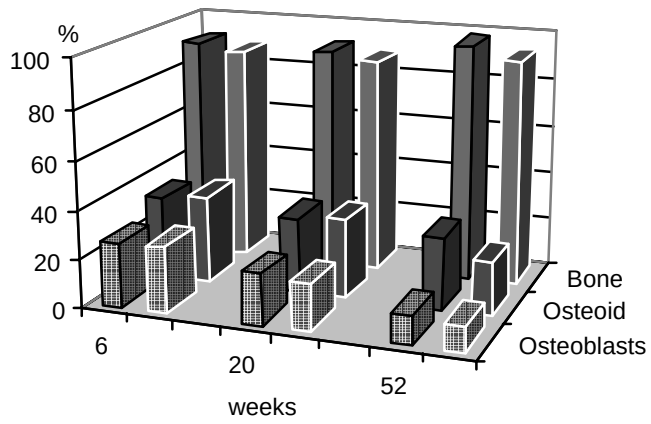
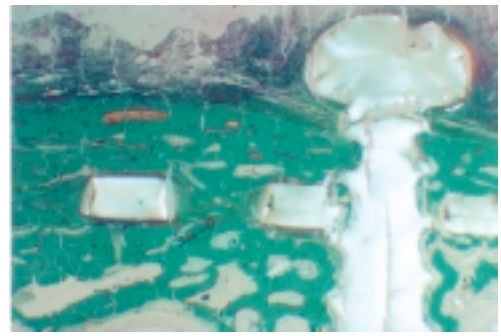


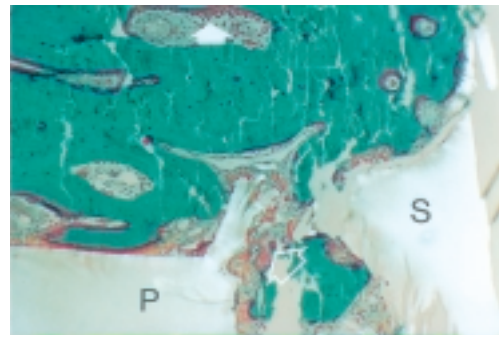
Figure 12. Intraosseous implantation of SR-PLLA plates in sheep calvarial bone: histomorphometric analysis on the implanted (columns with black border) and non-implanted sides (columns with white border). Analysis included bone tissue (total trabecular bone volume fraction including calcified trabeculae and osteoid of the total bone volume), osteoid (the total osteoid surface fraction of the total trabecular bone surface), and osteoblasts (the active osteoid formation surface fraction of the total osteoid surface, i.e. osteoid surface covered by active osteoblasts).

Figure 13.

A: Photomicrograph of an intraosseously implanted SR-PLLA plate, fixed with an SR-PLLA miniscrew, 20 weeks after operation in polarized light.

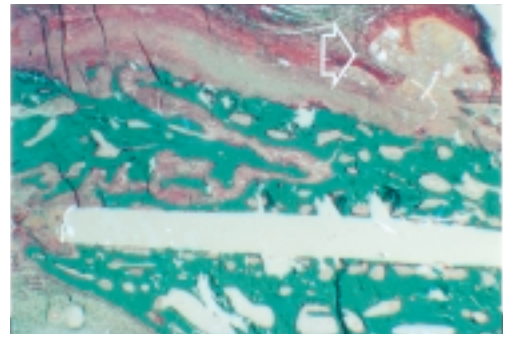


B: The area between the plate (P) and the screw (S) in greater magnification. Note the fibrils of the plate surrounded by giant cells (open arrows). Bone tissue grows between the screw and the plate. The surrounding growing and remodelling bone contains abundant osteoid (red lines) and osteoblasts (solid arrows).



C: AT 52 weeks, the plate is largely in direct contact with bone tissue. The screw head, located in subcutaneous tissue, has been fragmented.

Masson-Goldner trichrome, magnification x 16 (A,C), and x 40 (B). Reproduced by kind permission of *Journal of Craniofacial Surgery* from 9 (1998) 171-176.



largely in direct contact with bone tissue.

From 6 to 20 weeks, the implants looked intact. Multinucleated phagocytosing giant cells or osteoclasts, were present in the tissue-implant interface and on the remodelling trabeculae. A few lymphocytes were seen in the screw thread-connective tissue interphase, but neither lymphocytic infiltration nor neutrophilic granulocytes were evident. At 52 weeks, the plate and the screw threads still looked intact, whereas the screw heads had fragmented and were being actively resorbed (Fig. 13). Tiny particles of the SR-PLLA material had been phagocytosed by macrophages and giant cells. Inactive giant cells were present on the intraosseal implant surfaces. Active giant cells were seen in the connective tissue-implant interface, as in earlier specimens.

Healing of cranial osteotomies fixed with flexible PLA96 plates and SR-PLLA or SR-PGA miniscrews versus rigid titanium miniplate fixation (IV,V)

No neurological symptoms, infections or clinical foreign-body reactions were seen.

MACROSCOPIC: The osteotomies were stable on palpation, and investigation showed no loss of fixation or even minimal dislocation of the bone segment in any animal. The SR-PGA screws degraded rapidly: at four weeks, all the screw heads had been replaced with vesicles 3 mm in diameter, 0.5-1.0 mm in height, filled with clear fluid, but the screw tips on the dural side were still palpable. All the vesicles and screw tips had disappeared by six weeks. The SR-PLLA screws retained their integrity until 52 weeks, when minimal accumulation of fluid was noted around the screw heads. The screw heads and tips were easily identifiable and hard on palpation (Fig. 14) until they became softened at 52 weeks, and they had disappeared at 104 weeks. The PLA96 plates integrated with the surrounding contours and were hardly identifiable at 26-52 weeks. They fragmented to a yellowish powder-like thin layer in a year (Fig. 14C) and had disappeared by two years. Titanium plates and screws had translocated passively into the bone tissue and frontal sinus at 52-104 weeks.

MRI: Magnetic resonance imaging confirmed that no signs of complications such as displacement of the osteotomized bone, osteitis, gross inflammation at the osteotomy area or signs of liquor leakage were visible. The resolution of the MR images was insufficient to allow detailed evaluation of the biodegradable fixation system or the dural and cortex areas. We recommend a surface coil in assessing superficial areas of biodegradable minifixation with MR imaging.

Consolidation

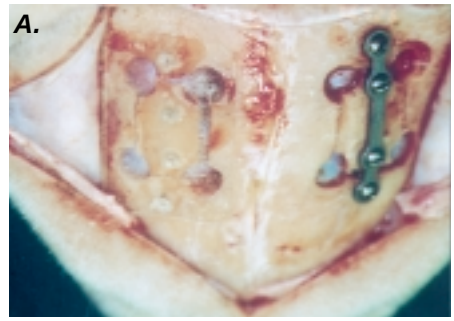
RADIOGRAPHY: In AP radiography, no displacement of the osteotomized bones was observed. Consolidation of the craniotomy lines was slow and incomplete (Fig. 15). At four weeks, only 7.3% of the craniotomy lines appeared to be consolidated on the SR-PGA side and 9.3% on the titanium side, and at 26 weeks the figures were 31.8% (SR-PGA) and 33.7% (titanium). Complete consolidation was not seen in any specimen. Most trephine holes had consolidated on both sides by 26 weeks without significant differences between covered (PLA96 plate) and uncovered (titanium plate) sides.

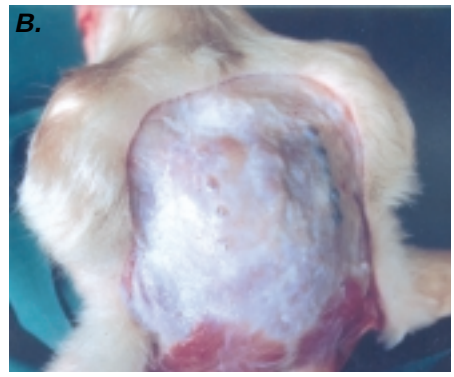
At 6 weeks, 7 out of 8 SR-PGA screw holes had enlarged from an original 1.5 mm to 1.6-2.0 mm, which was considered as a sign of osteolysis and was histologically verified. The borders were sharp, and no new bone formation was observed. From 12 weeks onwards the SR-PGA screw holes decreased in size ($p<0.05$), new bone formation was observed, and at 52 weeks the holes were filled with bone. The SR-PLLA screw holes at 104 weeks were sharp-edged, and 1.1 mm in diameter (original 1.5 mm). No reactions around the titanium screws were observed.

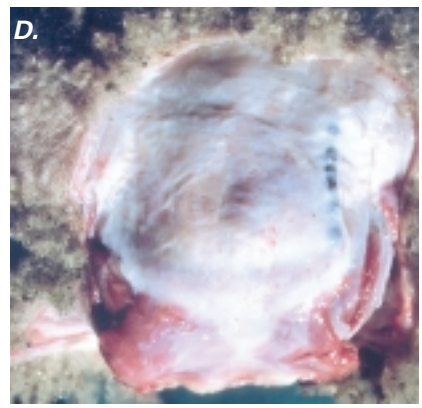
HISTOLOGY AND HISTOMORPHOMETY: Histological cross sections revealed irregular bone growth from the

Figure 14.

Sheep craniotomy areas at the time of operation **(A)** and postoperatively after sacrifice, dissected free of soft tissues at 26 **(B and C)** and 52 weeks **(D)**. The PLA96 plate is hardly identifiable, but the SR-PLLA screws are palpable both on the plate (B) and dural (C) sides. The SR-PLLA screw tips are covered by a thin tissue layer, but the titanium screw tips have penetrated the dura (C). Note the tiny impressions in the brain tissue caused by the SR-PLLA and titanium screw tips (C). At 52 weeks, the PLA96 plate is yellowish (D), and despite active bioabsorption, no clinical foreign body reaction can be seen. The SR-PGA screws have disappeared completely.







bony margins, very slowly replacing the dense connective tissue filling the craniotomy line. During the first four weeks, approximately two thirds of the line consolidated, but thereafter, the consolidation process markedly slowed down. At 4-6 weeks, 25-38% of the original bone defect remained. At 12 weeks, the defects had diminished to 18% (SR-PGA), 9% (titanium) and 15% (SR-PLLA). The originally straight craniotomy lines became diagonal, especially on the resorbable fixation side, and the defects were connected to a hole existing in the resorbable plate in 9 of 13 oblique lines (5 SR-PLLA, 4 SR-PGA) observed in 6-12-week specimens (Fig. 16). The consolidation pattern varied between the follow-up groups, especially in the SR-PGA-fixed group at 26 weeks (Fig. 17). These two sheep had iatrogenic dural defects with a piece of dura attached to the osteotomized bone segments. The lesions had healed incompletely and had led to local 3-7 mm-wide and 1-5 mm-high herniations of the brain tissue and resorption of bone over the lesion. However, the outer

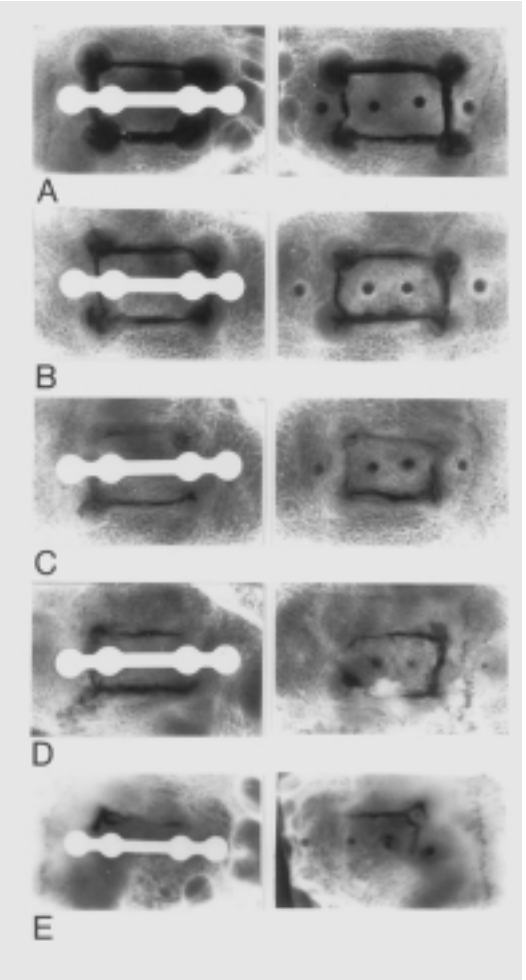


Figure 15.

Plain AP radiographs of the osteotomies 4 (A), 6 (B), 26 (C), 52 (D) and 104 (E) weeks postoperatively. Titanium fixation on the left, PLA96 plate and SR-PGA (A-D) or SR-PLLA (E) miniscrew fixation on the right. Reproduced by kind permission of *Journal of Neurosurgery*, from 90 (1999) 910-917.

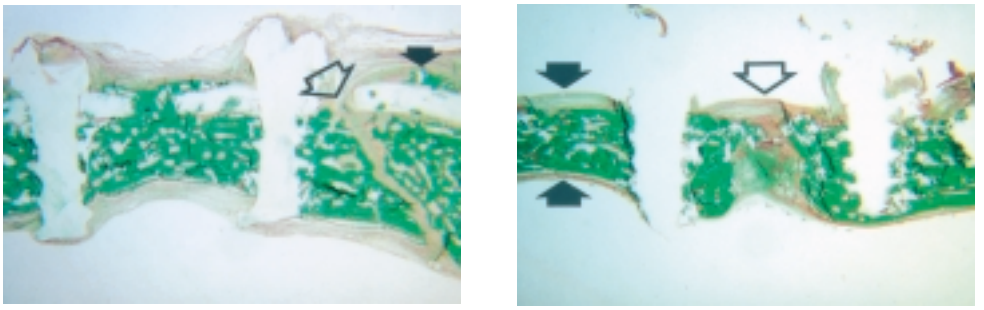


Figure 16. Photomicrographs of consolidating craniotomy lines 26 weeks postoperatively. ***Left:*** Osteotomy fixed with a PLA96 plate and SR-PLLA miniscrews. Note ingrowth of dense connective tissue through the hole in the plate (open arrow) and bone growth over the plate (black arrow). ***Right:*** On the rigidly fixed titanium side, the osteotomy line is straight (open arrow) and filled with connective tissue. The fixed bone segment is thin (black arrows). Masson-Goldner trichrome, magnification x 11.5.

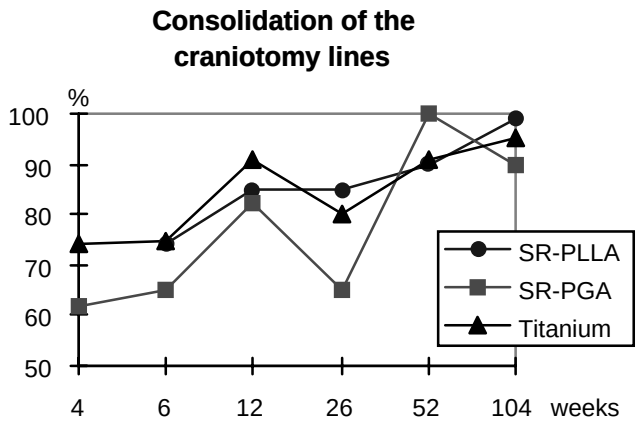


Figure 17. Histomorphometric analysis of the consolidation of osteotomy lines in different fixation groups. The results are given as mean values of the consolidated area of the original bone defect area.

bone surface was smooth on both sides, and no signs of fistulae or cerebrospinal fluid leakage were seen. In these particular animals, the non-consolidated craniotomy lines were large (24-47% of original) and there was reduced new bone (osteoid) formation in the craniotomy lines. At 104 weeks, histologically incomplete consolidation was observed in the SR-PGA-group (5%) and in the titanium group (rough estimate 10-15%).

Osteoid formation

In the non-operated control areas, new bone formation declined ($p<0.05$) along with maturation of the bone tissue (Fig. 18). In the operated bone area, continuous osteoid formation, as a sign of new bone formation and remodelling, was noted in all types of fixation. New bone formation was most active in bone areas adjacent to the dura, with 68-100% osteoid-producing trabecular bone surface. In the middle of the consolidating osteotomy lines, osteoid formation was less active, 32-80%, and on the plate and periosteum sides, as low as 20-58%. In areas with dural lesions (SR-PGA-fixed group at 26 weeks), osteoid formation was minimal (10-23%), when compared with adjacent intact dura, where the osteoid surface fraction was 68-82%. In the long term, total osteoid production was higher on resorbable sides than titanium sides, in which local bone growth was restricted.

Consistent and high osteoid formation appeared to result in increased thickness of the osteotomized bone segment (Fig. 19). On the resorbable side, bone was an average of 0.5 mm thicker than on the titanium side, and the difference was significant in the SR-PGA fixation group ($p<0.01$). No significant difference in thickness was observed between the resorbable fixation groups.

SR-PLLA and titanium screw areas showed continuous osteoid formation and differed significantly from control areas

($p<0.05$), but not from each other. In the SR-PGA screw areas, osteoid formation varied significantly ($p<0.01$) between the follow-up groups: during the most active bioabsorption period, from 4 to 6 weeks, it remained very low, but later it increased between 6 and 12 weeks ($p<0.001$), decreased again between 12 and 26 weeks ($p<0.01$), probably because of iatrogenic dural lesions observed in 26-week specimens, and increased from 26 to 52 weeks ($p<0.01$) (Fig. 18). Osteoid formation in SR-PGA screw areas differed significantly from that in control areas ($p<0.005$) and from that on the contralateral titanium side ($p<0.05$).

Biocompatibility and biodegradation

THE PLA96 PLATE was encapsulated in connective tissue, which was thickest at 4-6 weeks and thereafter slowly thinned and matured. A few giant cells, macrophages and lymphocytes were found on the implant surface. At 12 weeks, bone growth on the plate was observed, and inactive giant cells lined the bone-covered plate. At 26 weeks the PLA96 plate had become wavy and was surrounded by a 0.5 mm-thick fluid layer, which contained active giant cells, macrophages, lymphocytes and plasma cells. Macrophages and giant cells were penetrating cracks in the plate. The edges of the plate were covered by a thin bone layer, and in these "protected" areas, the capsule around the plate was thin and inactive (Fig. 16). At 52 weeks, the plate had become fragmented and hydrolysed (Fig. 20A), and the polymeric debris was encapsulated in mature, densely vascularized connective tissue and was undergoing resorption by foamy macrophages and giant cells (Fig. 20B). The bone surface was microscopically irregular and lacking osteoid under the resorptive areas. At 104 weeks, the entire PLA96 plate had disappeared (Fig. 20C). The bone surface was smooth and covered with dense, abundantly vascularized connective tissue. In the specimen with SR-PLLA screw material, giant cells, with intracytoplasmic polarizing material, were found in the connective tissue layers in areas of former plate. In the specimen with SR-PGA miniscrews and a PLA96 plate, there were no signs of a foreign-body reaction or remaining polymer (Fig. 20C).

SR-PLLA MINISCREWS: From 6 to 26 weeks, the configuration of the screws was sharp, and the head-shaft junction solid (Fig. 21A). A mild foreign-body reaction (FBR) consisting of one scattered cell layer of macrophages and giant cells delineated the entire screws, and formation of osteoid (remodelling) was active around the screw threads. The dura tightly followed the configuration of the screw tips (Fig. 21A). At 26 weeks, accumulations of macrophages were seen around the whole screw head, and weathering and cracking in the screw threads were seen. At 52 weeks, two screw heads had become loose from the threads and were lying tilted in bony grooves (Fig. 21B), and were undergoing fragmentation and resorption. The resorptive area, filled with hydrolyzing and degrading polymeric material and a thin fluid layer, was surrounded by an abundant zone of foamy macrophages and giant cells, then by a thin zone of lymphocytes and farthest out, a mature connective tissue capsule. At 104 weeks, remnants of polylactide particles were found scattered on the bone surface and in the screw channels, surrounded by giant cells,

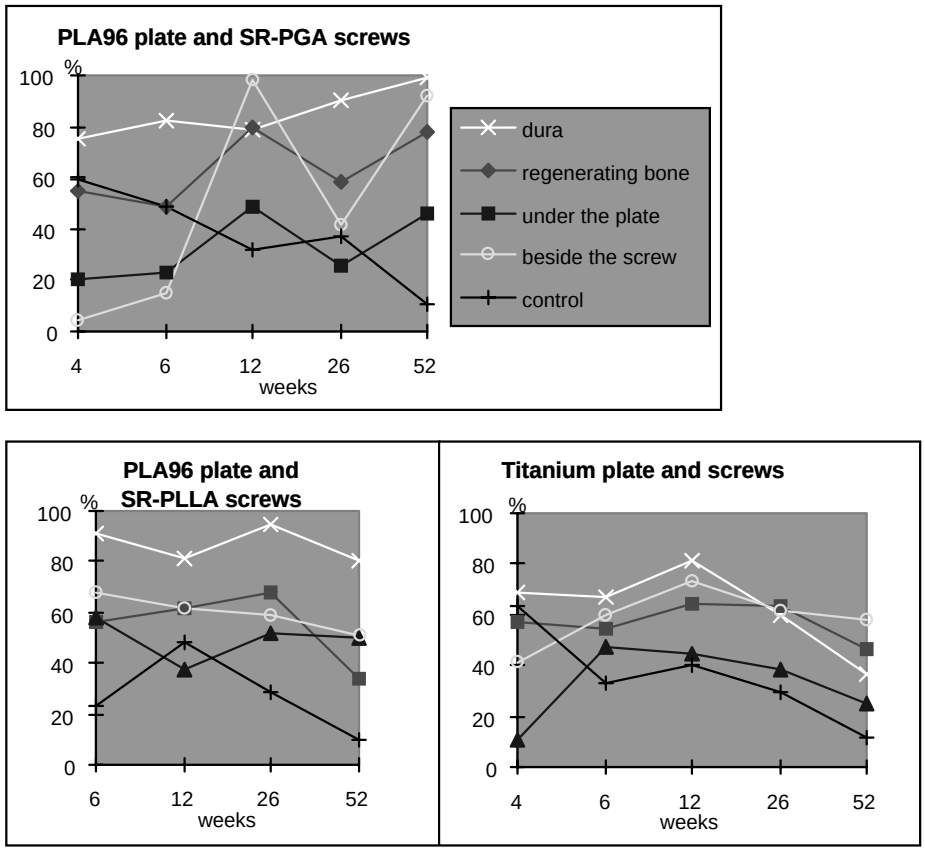


Figure 18. Histomorphometric measurements of osteoid surface fraction over total trabecular bone surface in lamb craniotomy. Five specific areas were examined (adjacent to dura, in the middle of the regenerating bone margin, under the plate, beside the screw and in the control area) and the results are shown separately in each of the three fixation groups.

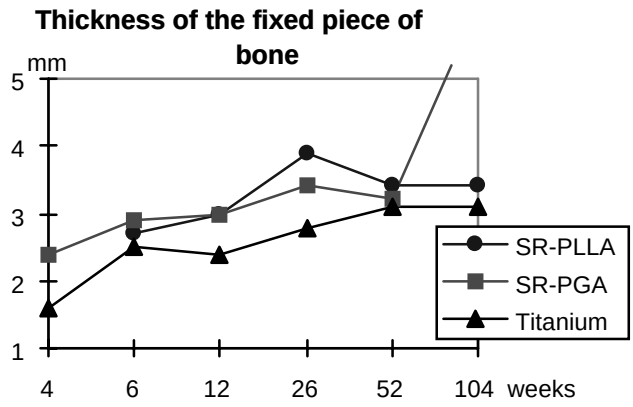


Figure 19. Lamb calvarial osteotomy: mean thickness of the repositioned and fixed bone segment in different fixation groups.

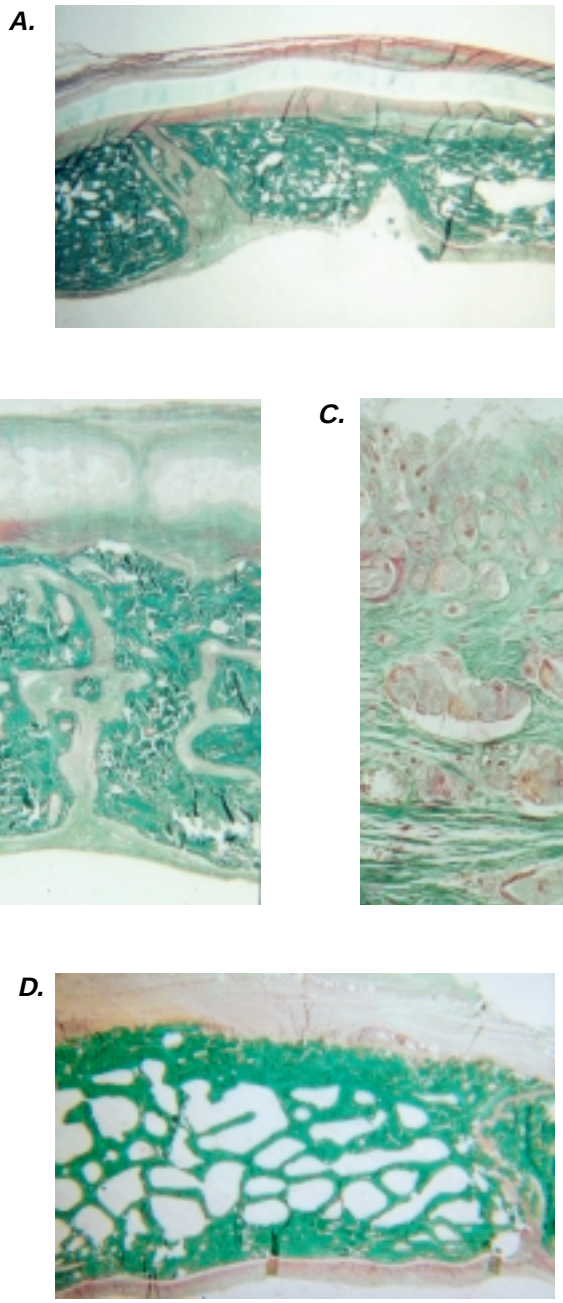


Figure 20. Photomicrographs showing biodegradation and bioabsorption of PLA96 plates. At 26 weeks **(A)**, the plate was wavy and surrounded by a thin layer of fluid and a mature connective tissue capsule. By one year **(B)**, the plate had become fragmented and partly hydrolysed. **(C)** A connective tissue capsule surrounded the polymer, and macrophages and multinucleated giant cells (arrow) can be seen around the polymeric debris. Even intracytoplasmic polymer can be seen in these cells. At two years **(D)**, the plate, polymer, SR-PGA miniscrews and foreign-body reaction had disappeared completely. Masson-Goldner trichrome, magnification x 5.6 (A,B,D) and x 250 (C).

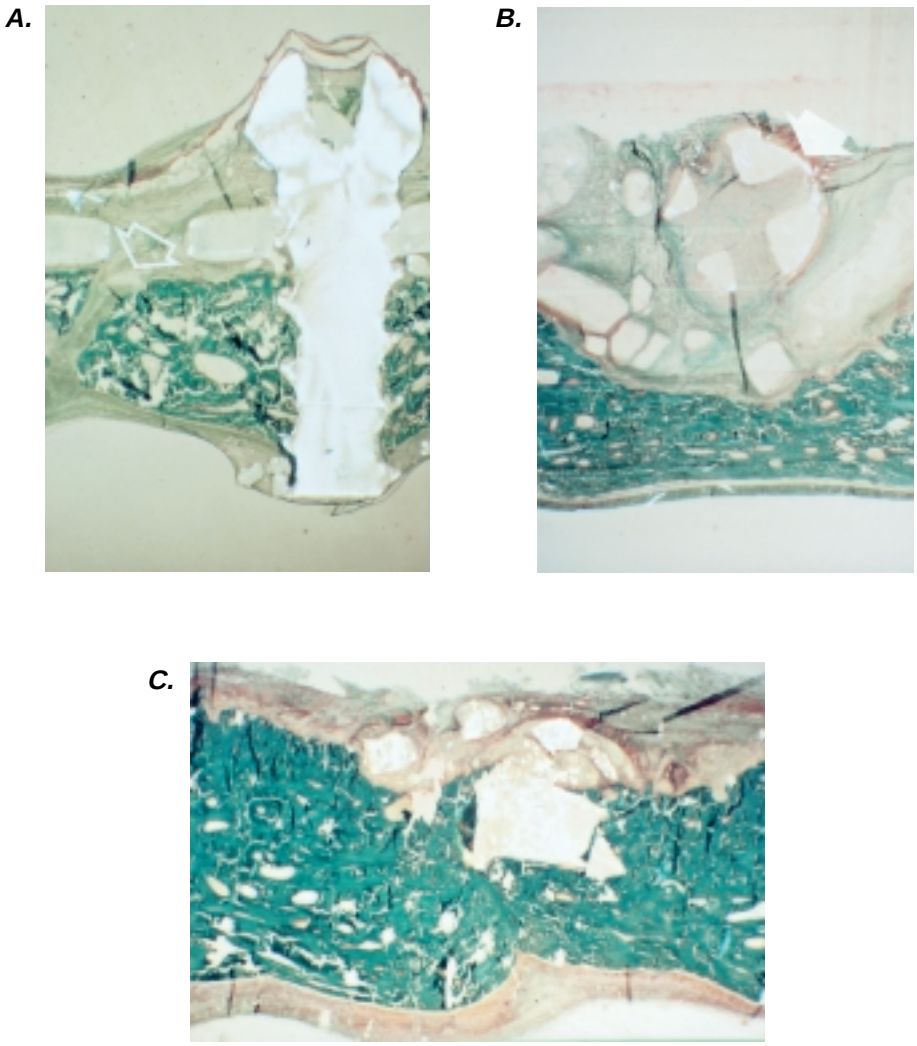


Figure 21. Photomicrographs showing the biodegradation of SR-PLLA miniscrews: At 26 weeks, the entire screw including the head-shaft junction is whole **(A)**. The dura is unbroken under the screw tip that has been shortened with an oscillating saw. Note connection between the connective tissue filled craniotomy line and hole of the plate (arrow). At one year (**B)**, the SR-PLLA screw heads (arrow) have loosened and lie tilted in bony grooves, on top of the more rapidly degrading PLA96 plate. At two years **(C)**, the SR-PLLA screws have fragmented, and slow bioabsorption proceeds with a mild foreign-body reaction. The biodegradable screws have not translocated, and the dura is unbroken throughout the follow-up time. Masson-Goldner trichrome, polarized light, magnification x 17.5.

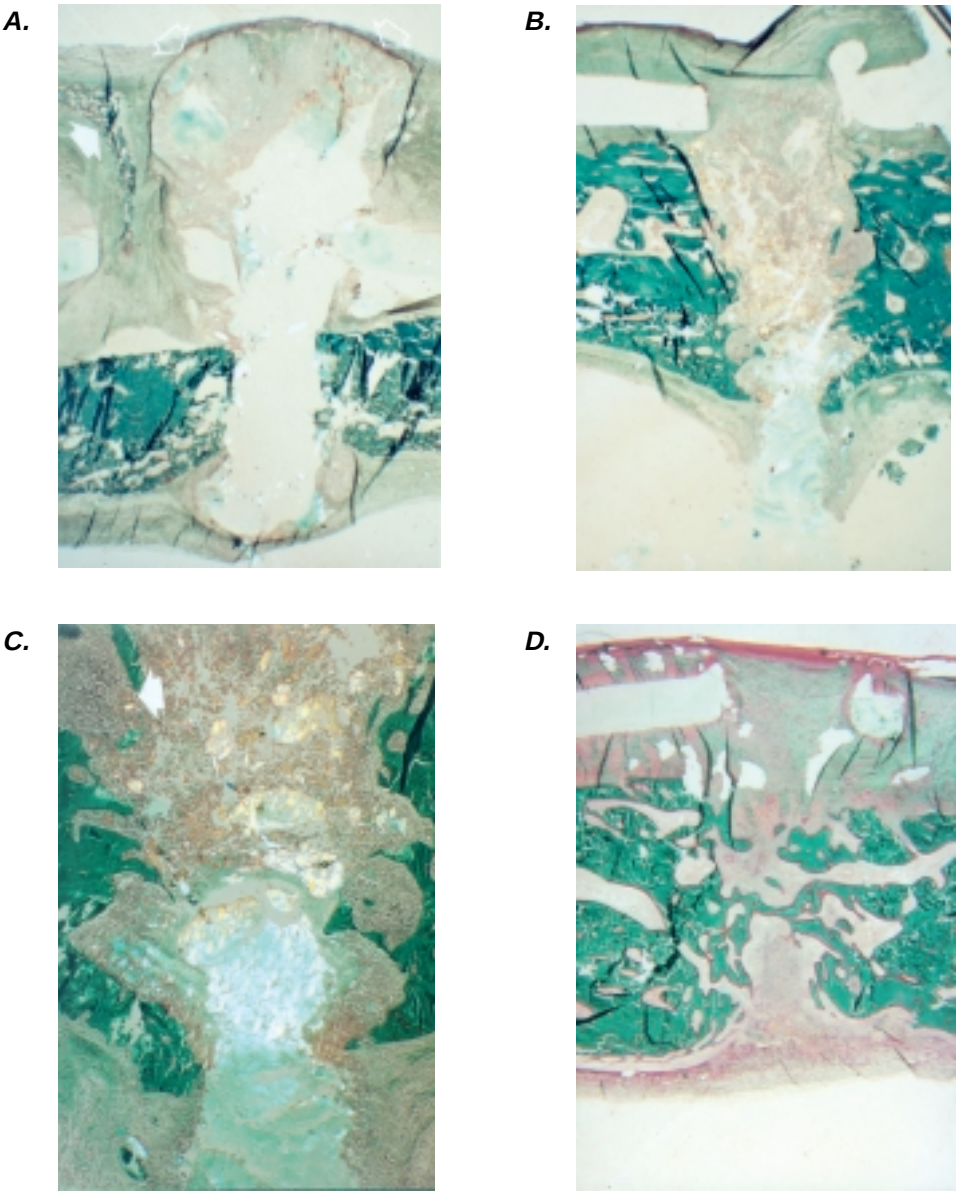


Figure 22. Photomicrographs of the biodegradation and bioabsorption of SR-PGA miniscrews. At 4 weeks **(A)**, the screw has hydrolysed and the swollen screw head is surrounded by a connective tissue capsule (open arrows). Note bone formation in the connective tissue capsule (solid arrow). At 6 weeks **(B)**, the screw head has disappeared, the screw channel is enlarged, and polymeric debris extends beneath the dura. Polarized light shows PGA particles in the screw channel, extending beneath the dura. Greater magnification **(C)** shows a typical non-specific foreign-body reaction and a few lymphocytic infiltrations (arrow). At 12 weeks **(D)**, the polymer has disappeared almost completely, and the screw channel is vigorously remodelling and filling up with bone tissue rich in osteoid (red surface on the bone trabeculae). The dura has regenerated. Masson-Goldner trichrome, magnification x 17.5 (A,B,D) and x 35 (C). Reproduced by kind permission of *Journal of Cranio-Maxillofacial Surgery*, from 27 (1999) 42-50.

foamy macrophages and a dense connective tissue capsule (Fig. 21C). On the bone surface, tiny 0.1-0.5 mm-deep grooves filled with giant cells containing intracytoplasmic polymeric material were found. The dura was continuous throughout the follow-up time. In 52- and 104-week specimens, thick bone layers had formed under the cut screw tips, isolating them from the dural tissue.

SR-PGA miniscrews: At four weeks, the screw heads had become fragmented and hydrolysed and were surrounded by clear fluid (Fig. 22A). This fluid accumulation was limited to the stretched connective tissue capsule formed around the screw head and there was an intense FBR, reflected in the presence of macrophages and giant cells, and a minor inflammatory reaction with lymphocytes. The intraosseal screw thread was still whole, surrounded by connective tissue, lymphocytes and few neutrophilic granulocytes, and the dura was continuous and attached to the screw tips. At six weeks, the entire screw head had been resorbed (Fig. 22B). Thin laminar layers of FBR-associated cells and PGA fragments were found in the connective tissue layers running parallel to the plate. The hydrolysed and partly resorbed screw thread was surrounded by loose connective tissue containing lymphocytes, macrophages, giant cells and a few plasma cells (Figs. 22B,C). A 6 mm-long, non-shortened screw had penetrated the dura, and a similar FBR around polymeric particles was seen on the dural side (Fig. 22C). The screw channels had enlarged (Fig. 23). At 12 weeks the former screw channels could be identified because they were shrinking and vigorously remodeling (Fig. 22D), and a few foamy macrophages and giant cells with intracytoplasmic, polarizing PGA could be seen. The dural tissue was continuous and thick in areas of former screw tips. At 26 weeks, the FBR had nearly disappeared, and occa-

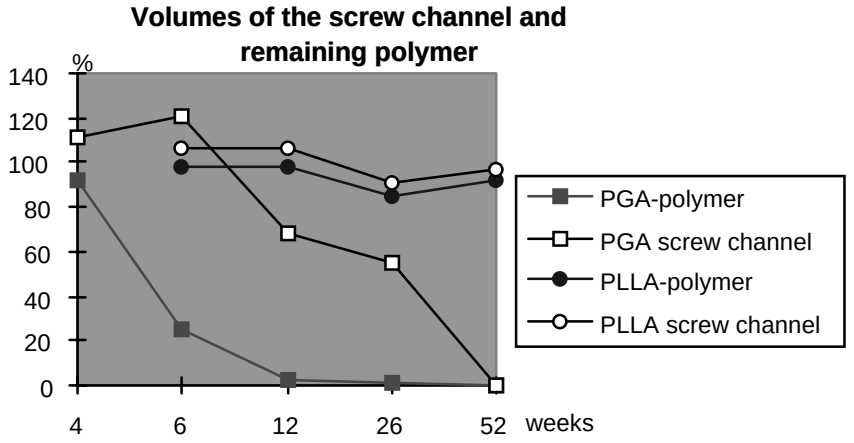


Figure 23. Histomorphometric measurements of the volumes of the screw channels and remaining polymer inside the channels (both as % of original) after implantation of SR-PLLA and SR-PGA miniscrews in lamb calvarium.

sionally a few PGA particles were found in the remodelling bony trabeculae. At 52 weeks, the screw channels could not be distinguished in the dense bone tissue, and the FBR had terminated in the channels and on the dural side. At 104 weeks, no extra- or intracytoplasmic PGA remnants were found in histological sections.

Titanium implants: The connective tissue capsule around the implants was very thin, and giant cells were found on the implant surfaces only occasionally. Throughout the follow-up time, the FBR was minimal. At 4 weeks, bone remodelling was seen around the screw threads. The screw tips (dural side) were surrounded by macrophages and a few lymphocytes. At 6-26 weeks, a few giant cells, macrophages and lymphocytes were found around the implants, the amounts diminishing with time. At 52-104 weeks the screws were mostly in direct contact with bone tissue, and a few titanium particles and lymphocytes were found scattered in the connective tissue layer. Dural continuity was broken where the screw tips were long or translocated.

	SR-PLLA plate,0.5 mm, perforated	**PLA96** plate, 0.4 mm, perforated	**SR-PLLA** 2 mm miniscrews	**SR-PGA** 2 mm miniscrews
Signs of biodegradation	1 year	26 weeks	1 year	< 4 weeks
Most active bioabsorption	2 years	1 year	2 years	4-6 weeks
Complete bioabsorption	> 2 years	2 years	> 2 years	< 1 year
Foreign-body reaction:				
-soft tissues	max. + at 2 years	max. + at 1 year	max. + at 2 years	max. ++ at 4 weeks***
-intraosseal	-	-	max. (+) at 1 year	max. +++ at 6 weeks
Osteolytic reaction	-	-	-	max. ++ at 6 weeks

- absent
(+) very mild (occasional macrophages and/or giant cells)
\+ mild (a few macrophages and giant cells)
++ moderate (macrophages, giant cells, a few monocytes/lymphocytes)
+++ distinct (macrophages, giant cells, plasmacells, monocytes, lymphocytes)
*** slight fluid accumulation, observed only during dissection

Table 6. Summary of the biodegradation and bioabsorption rates of the bioabsorbable implants used in the present study.

GENERAL DISCUSSION

In paediatric craniofacial surgery, bioabsorbable osteosynthesis materials have become not only a choice among other fixation techniques, but even a recommendation (*Habal* 1996). The materials used in the present studies reflect the development of bioabsorbable miniosteosynthesis devices. First generation materials, pure PLLA and PGA, have been replaced by their copolymers and stereocopolymer P(L/DL)LA, which have more ideal bioabsorption characteristics. The mechanical qualities can be significantly improved even in mini-implants by the self-reinforcing technique (*Törmälä* 1998).

In the literature, bioabsorbable materials have been particularly recommended for fixation of osteotomies in the growing neurocranium, but there is only one published experimental study on fixation of unstable craniotomies with bioabsorbable plates (*Illi et al.* 1990). Most earlier experiments have been performed on the viscerocranium or endochondral bones. Operating on the neurocranium is more time consuming, requires special instrumentation and is subject to fatal complications. The results of earlier studies on viscerocranial osteosyntheses may not be directly applicable to osteosyntheses in the neurocranium. In addition, wide variability and insufficient information on the fixation materials adds to the difficulty of interpretation and comparison with the results of earlier experimental studies.

Material and methods

Despite being young and growing, the sheep were not of the same age in the three experiments, which may have caused variability in the results. Histological sections of the dense cranial bone were of good quality, and the staining method was succesful which enabled very exact histological and histomorphometric analyses of the specimens. Because of the high quality of the histological sections, OTC-fluorescence studies and microradiography did not add greatly to the information, and were not performed in later experiments. Plain film radiographs, CT and MR images corresponded to clinical situations.

The experimental designs were simple, in order to avoid surgical complications, to limit variability of the results and to allow detailed, comparative analysis of the consolidation process and biocompatibility and biodegradation of the bioabsorbable implants. In orthopaedic and most maxillofacial experiments, fractures or osteotomies have usually been exactly repositioned before fixation, because contact between bone edges is essential for bone healing and prevention of non-union. In reconstructive paediatric craniofacial surgery, bone defects in the form of narrow craniotomy lines, trephine holes or larger, are an unavoidable consequence of surgery. Consolidation of craniotomy lines has not previously been studied experimentally,

possibly because it has been considered to be uneventful.

In the first experiment, the only stress on the plate was slow completion of skeletal growth. In the third experiment, the osteotomized bone segments were completely detached from surrounding tissues and reinserted and fixed without bony contact with the surrounding bone tissue, and the stresses were a combination of intracranial pulsative pressure, skeletal growth, and occasional external forces. Specific findings in these animal models may not be directly equivalent to that observed in paediatric craniofacial surgery, as in clinical craniofacial operations, pieces of bone are preferably set together with as much bony contact as possible to ensure stability and consolidation. On the other hand, the bone defects created in craniofacial surgery may be considerably larger than 2.3 mm-wide craniotomy lines or 6 mm-wide trephine holes. The experiment with intraosseal plating was the first of its kind published in craniofacial surgery, and reflects the development of new surgical techniques based on new bioabsorbable osteosynthesis devices.

Bone healing

Loss of fixation, or instability, did not occur. No complications caused by the resorbable osteosynthesis devices were observed during the 4-104-week follow-up periods. Passive translocation of the resorbable devices did not occur.

In the first study in older sheep, the stable osteotomy lines plated with narrow titanium implants showed a consolidation pattern with bulky, uneven masses of bone, and complete osseous healing was seen only in the 104-week sample, whereas the SR-PLLA-plated osteotomies had consolidated by 20 weeks. In the third experiment, in younger sheep, no such striking differences in healing of the resorbable and titanium-fixed osteotomies was noted. The narrow craniotomy lines surrounding the devascularized bone segment consolidated slowly and incompletely, independent of the type of fixation. During the first 4 weeks, 60-70% of the original bone defect had consolidated, but thereafter, consolidation remarkably slowed down. The craniotomies were stable on palpation, and the signs of incomplete and delayed consolidation were histological.

According to experienced clinicians, most osteotomies in infants heal rapidly (*Lauritzen, personal communication* 1999). Thus, slow consolidation in the present experimental models was unexpected. As regards incomplete consolidation, dural lesions could be an explanation, but the dura was intact in all but two cases. The osteogenic importance of young dura was emphasized in those two cases, which is in line with earlier experimental and clinical reports (*Mossaz and Kokich* 1981; *Winston et al.* 1983; *Hobar et al.* 1993). New bone formation was most active in bone areas close to undamaged dura.

Stability of fixation did not appear to be of crucial importance for consolidation, as the first experimental osteotomies were absolutely stable but consolidation was incomplete, and in the third experiment, rigid and semi-rigid fixation had no significantly different effects on consolidation. Local restriction of growth can cause growth disturbances, which has been documented experimentally with rigid metallic fixation (*Lin et al.* 1991; *Yaremchuk* 1994; *Polley et al.* 1995). There is no evi-

dence in the literature indicating that consolidation of a rigidly restricted bone defect in growing animals may be impaired because of the rigidity. Local bone growth was certainly restricted on the titanium side in lamb craniotomies, which has been proven earlier in several studies (*Lin et al.* 1991; *Yaremchuk* 1994; *Polley et al.* 1995; *Polley et al.* 1998). In addition, titanium-fixed bone segments remained thinner than non-rigidly and transiently fixed bone segments, which has also been shown earlier (*Thaller et al.* 1996). However, the trabecular bone volume in the fixed piece of bone remained high independent on the type of fixation, which is in contrast to a previous report (*Kennady et al.* 1989a). As in previous reports, passive translocation of the metallic implants into the bone and the frontal sinus was observed (*Fearon et al.* 1995; *Goldberg et al.* 1995; *Honig et al.* 1995; *Papay et al.* 1995; *Yaremchuk and Posnick* 1995; *Persing et al.* 1996).

Guided bone regeneration (GBR) has been demonstrated to be effective in osteopromotion and prevention of fibrous nonunion in craniofacial bone defects (*Gottlow et al.* 1984; *Dahlin et al.* 1988; *Dahlin et al.* 1991; *Gottlow* 1993; *Karring et al.* 1993; *Linde et al.* 1993; *Lundgren et al.* 1995; *Mooney et al.* 1996;*Lemperle et al.* 1998), and seemed to be of greater importance in older animals in the first experiment. Periosteum alone (without any other membrane) has been considered to function as a biologically active membrane (*Engdahl* 1971; *Linde et al.* 1993), but in the present experiment, the role of periosteum was inferior to that of the SR-PLLA plate. Connective tissue invasion might be the explanation for the lack of ossification in clinical cases as well. In the third experiment, a large, thin PLA96 plate covered the whole osteotomy and bone defect area in young lambs. Nevertheless, connective tissue invasion was rapid and occurred freely through the holes in the PLA96 plate. Consolidation of the trephine holes covered with a PLA96 plate was slightly better than in the titanium-fixed craniotomies, but the difference was not statistically significant. Dural and periosteal sides of the osteotomy lines did not show significant differences either. Thus, the role of GBR might be more important in older animals with diminished dural osteogenic capacity.

Biocompatibility and biodegradation

In the present study, clinically significant foreign-body reactions, such as swelling or seroma, or infection, did not occur in the 1-2 year follow-up periods. The biocompatibility of SR-PLLA implants was good: Intraosseously implanted SR-PLLA plates became integrated with the bone tissue, and the connective tissue capsule surrounding the implant slowly thinned and partly disappeared, resulting in direct contact between the implant and bone. Koskikare *et al.* used two identically manufactured, equally thick but non-perforated SR-PLLA plates for intraosseal fixation of rabbit distal femoral osteotomies (*Koskikare et al.* 1996). The amount of bone was greatest near the plates and especially strong between them (*Koskikare et al.* 1997). Growth of bone tissue into the holes of a plate probably strengthens the osteosynthesis by uniting the bone layers separated by the plate. Thus in an intraosseal environment, perforated plates might be more advantageous than non-perforated ones.

Earlier experiments have shown that the degradation kinetics of biodegradable implants depend on the site of implantation, probably because of differences in tissue perfusion (*Tschakaloff et al.* 1994). In the present study, subperiosteally implanted SR-PLLA plates and screw heads started to fragment in one year and resorb in two years. Intraosseal plates and screw parts, embedded in extremely dense calvarial bone, degraded more slowly. The subperiosteal implants, especially screw heads, were also prone to mechanical stress because of the butting habit of the animals. The foreign-body reaction was also milder around intraosseal than subcutaneously located parts of SR-PLLA implants, which is in accordance with the results of earlier studies (*Päivärinta et al.* 1993; *Suuronen et al.* 1994; *Böstman et al.* 1995).

Plates manufactured of high molecular weight, as-polymerized PLLA have caused striking foreign-body reactions (*Bergsma et al.* 1993; *Bergsma et al.* 1995). As-polymerized material is not very well purified, which may have contributed to the disappointing results, in addition to the thickness of the relatively weak, non-reinforced plates (2 mm) and subcutaneous implantation under thin facial skin. Bioabsorption of the PLA96 plate in the present study was complete by two years, without the slightest clinical foreign-body reaction. Degradation of this stereocopolymer is considerably faster than that of pure poly-L-lactide.

In the present study, no adverse reactions to SR-PGA miniscrews were noted clinically, but transient, subcutaneous, tiny vesicles had developed in hydrolyzing miniscrew head areas at four weeks. They had disappeared by the sixth postoperative week, probably because the implants used were considerably smaller than those used by Böstman *et al.* (1990), and were located in abundantly vascularized tissue in a growing animal. As in earlier studies (*Böstman et al.* 1992a; *Böstman et al.* 1992b), a minimal transient osteolytic reaction was also observed in the present study, but compensatory, extremely active new bone formation and remodelling followed. Bioabsorption of a polymer activates the monocyte-macrophage-giant cell line. Giant cells and osteoclasts are very difficult to distinguish from each other and may even be the same cells (*Wang et al.* 1997), and activation of giant cells in bone tissue might lead in practice to activation of osteoclasts, which may result in decreasing osteoid formation or even transient osteolytic reactions during absorption of the polymer. Osteolytic reactions have been associated with the use of PGA implants in adults (*Pelto-Vasenius et al.* 1997), whereas in children, no adverse effects have been reported (*Mäkelä et al.* 1992). In the present study, PGA debris was extruded from the enlarged channel to the subdural space. The fluid here reflected a typical non-specific foreign-body reaction without signs of infection, supporting the results of earlier studies in other than calvarial tissues (*Herrmann et al.* 1970; *Böstman et al.* 1992a; *Böstman et al.* 1992b; *Thaller et al.* 1995b). In addition, the dural lesions caused by screw tips completely regenerated after resorption of the polymer.

The rate of bioabsorption of PLLA was too slow, and that of PGA too fast in sheep cranium, whereas that of PLA96 was acceptable. The SR-technique enables manufacture of mechanically strong implants with relatively reduced polymer volume and small implant size, which further add to the biocompatibility and clinical appli-

cations. Because of the high initial strength, SR-implants can be sterilized with gamma irradiation, which has been shown to decrease molecular weight and thus fasten the degradation process (*Claes et al.* 1996). Gamma irradiation has been considered safer than sterilization with ethylene oxide (*Nair* 1995), which has been used for sterilization of non-SR-implants.

Fixation properties and strength retention

Until the development of self-reinforced implants, biodegradable plates were too bulky and thick to be inserted into the calvarium or other thin bones. When the biocompatibility and mechanical strength of implants are sufficient, the surgeon may choose the method of fixation according to the circumstances, free of concern as regards a removal operation. To be biomechanically safe, bioabsorbable implants should have 1) high initial strength to carry physiological loads during healing, 2) an appropriate initial modulus; not too stiff or too flexible for the special purpose required, and 3) controlled strength and modulus retention *in vivo*, in harmony with the increase of strength and modulus of the healing tissue (*Törmälä et al.* 1998). Very little is known about the biomechanical and deformational forces acting on the craniofacial skeleton under applied load conditions *in vivo*. The biomechanical demands that an infant neurocranium sets for fixation systems have been based on assumptions more than on biomechanical data.

Suuronen *et al.* have shown that 0.5 mm-thick but non-perforated SR-PLLA plates in four layers are strong enough for fixation of experimental mandibular fractures in sheep (*Suuronen et al.* 1992a). Six weeks postoperatively, the bending strength of the SR-PLLA-fixed mandibles was 88% of the intact control side, whereas that of titanium-fixed specimens was only 37%. After 12 weeks, the values were 90% vs. 75%, and at 24 weeks, 105% vs. 114%, respectively (*Suuronen et al.* 1992b). In our first experiment, consolidation of the stable bone slit was slower and the plate considerably weaker, although it was not prone to mechanical stress. Dense perforation weakened the plate markedly and enlarged the resorptive area. In this SR-PLLA plate prototype, the polylactide fibres run parallel, and the very thin plate may fracture between the uniaxially oriented fibres, especially between the perforations. This may have caused fracturing of the plate as early as at 6 weeks. In the new generation of SR-plates, this problem has been solved by biaxial orientation in a net-like fashion. They are also malleable in room temperature, which is especially appreciated by surgeons.

The initial strength of PLA screws (*Wittenberg et al.* 1991) and SR-PLLA screws (*Pohjonen et al.* 1997) has been considered comparable to that of metallic screws, and in the present study, both self-reinforced miniscrews could be properly tightened against the plate without torsional loosening of the screw head. The SR-system does not affect the hydrolytic timetable, which depends on the chemical composition of the polymer. Even minimal hydrolysis and degradation of an initially strong screw will result in loss of screw holding power (*Kellman et al.* 1994). The SR-PGA miniscrews had lost their holding power by four weeks, whereas the SR-PLLA miniscrews remained unchanged for 26 weeks. Early hydrolysis of the SR-PGA miniscrews al-

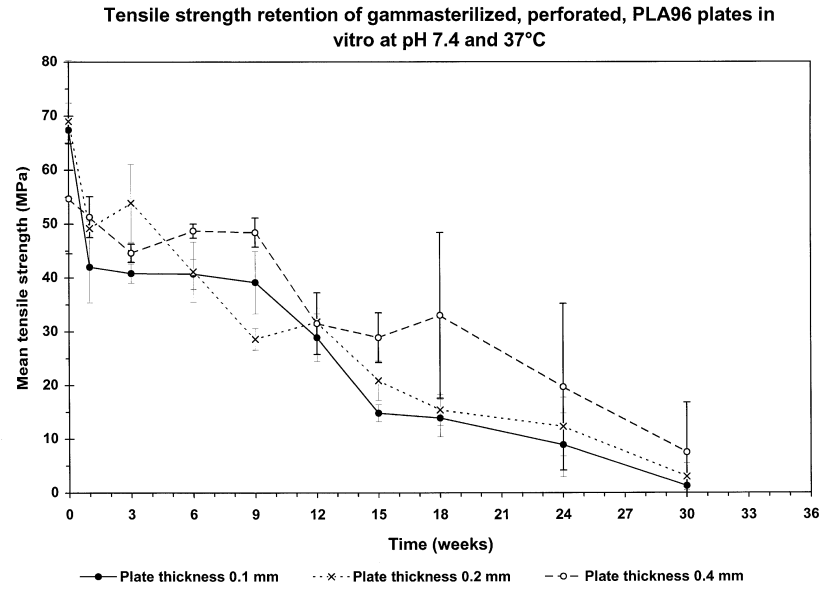


Figure 24. Tensile strength retention of the PLA96 plates used in the present study.

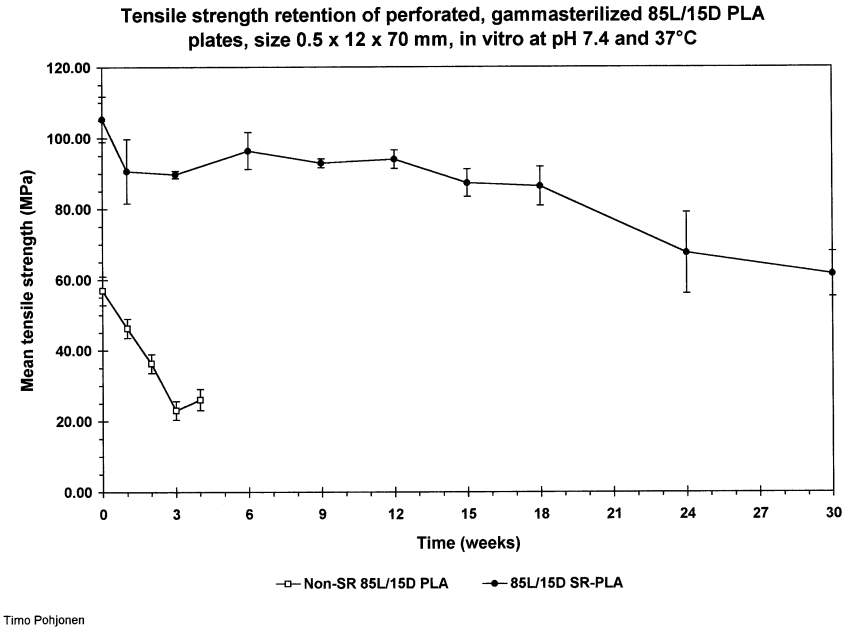


Figure 25. Tensile strength retention of non-SR and SR-P(L/DL)LA 70:30 plates.

lowed unrestricted local bone growth and skull expansion.

The initial strength of the experimental PLA96 plate and SR-PLLA miniscrews (design with third experiment) has been measured in cadaveric sheep skull by compressing the fixed bone segment from the outside (*Peltoniemi et al.* unpublished data). The non-reinforced, flexible 0.4 mm-thick plate reversibly yielded 4-5 mm before breaking at 74 N (mean), whereas fixation with four short metallic microplates and 8 microscrews irreversibly yielded 7-8 mm before breaking at 305 N. The resorbable plate tended to break along the osteotomy lines and through the screw holes, whereas none of the bicortically inserted SR-PLLA screws broke. The initial tensile strength of these plates was 54 MPa (Fig. 24). An identical osteotomy, fixed with 0.4 mm-thick SR-PLA thread, broke at 143 N (mean). Non-reinforced PLGA plate-screw fixation in sheep cadaveric calvarial bones has been reported to break at a distraction force of 270 N and a compression of 200 N, when measured on the *long axis* of the plate (*Gosain et al.* 1998). Even though the strength values between these two studies are not comparable, it would appear that the PLA96 plate should be reinforced, possibly biaxially, to be sufficiently strong and reliable for fixation of larger cranial osteotomies. Tensile strength of P(L/DL)LA plates can be significantly increased by the SR-method (Figure 25).

The fixation system should be initially strong enough to tolerate acute forces, possibly greater forces than 74 or even 200 N. Because of plasticity of infant neurocranium, a semi-rigid plate that maintains space and does not allow collapse, but allows minimal movement with return to its original position, might be preferable to a rigid plate. As the rigidity of fixation does not appear to be crucial, flexibility of the plate to some extent, with an ability to return to its original position could be an advantage in infant cranium. The bony frame of the cranium has to be reliably and rigidly fixed, but limited areas could be yielding.

Future research

Bioabsorbable plates and membranes may be useful tools in both guided bone regeneration and tissue engineering. Whether or not bioabsorbable membranes could be used for patching dural lesions, also remains to be studied. Materials that are intended for intraosseal or intracranial implantation should be studied as regards their biocompatibility in leptomeningeal and brain tissues.

A promising field of future research is the incorporation of osteogenic proteins (*Illi and Feldmann* 1998) into resorbable fixation materials, i.e. using the fixation material as a delivery system that would prevent soft tissue prolapse and maximize the interaction between the osteoinduction agent and osteoprogenitor cells, which would probably lead to enhanced bone regenerative capacity.

Clinical significance

The results of the present experiments cannot be adapted to clinical practice as such, but they emphasize the importance of testing new materials and methods of fixation in specific sites and conditions before clinical use.

In paediatric craniofacial surgery, rigid

metallic fixation can be replaced by bioabsorbable osteosynthesis devices. By using bioabsorbable mini-implants, we can avoid several disadvantages associated with metallic devices, such as the removal operation, growth restriction, irreversible passive intracranial translocation, extrusion, cold sensitivity, stress shielding and corrosion. New surgical techniques can be devised, as the placement of bioabsorbable fixation material is not a limiting factor. Radiolucency of these devices facilitates both postoperative follow-up (*Tschakaloff et al.* 1993; *Viljanen et al.* 1998) and radiotherapy after tumour surgery (*Rozema et al.* 1990b). Bioabsorbable implants with a great range of applications can be manufactured, and technological and medical co-operation is important for developing safe implants with ideal biomechanichal, mechanical and bioabsorption qualities.

SUMMARY AND CONCLUSIONS

The purpose of the present investigation was to study the biocompatibility of SR-PLLA and PLA96 miniplates and SR-PLLA and SR-PGA miniscrews in growing neurocranium and their suitability for fixation of calvarial osteotomies in sheep. The implants used in the present study were prototypes manufactured during the search for ideal bioabsorbable mini-implants. A total of 41, skeletally immature sheep were operated upon in three series of experiments. In the first, simple bilateral craniotomy lines served as an experimental model to study the basic consolidation process of a common bone defect in craniofacial surgery. The craniotomy lines were plated with an SR-PLLA plate on one side and a narrow titanium plate on the contralateral side, and both were fixed with titanium miniscrews. During the follow-up time of two years, the results of computerized tomography, plain film radiography, microradiography, histology, histomorphometry and fluorescence studies confirmed that bony consolidation was significantly more effective under the SR-PLLA plate, and the titanium-plated lines resulted in non-union. The SR-PLLA plate biodegraded in two years, but bioabsorption was incomplete.

In the second experiment, an SR-PLLA plate was inserted intraosseously in a bony slit sawn tangentially in the calvarium of six sheep, and fixed with a prototype SR-PLLA miniscrew. The plate showed excellent biocompatibility during the follow-up time of one year and it became integrated as part of the bone tissue in histological and histomorphometric studies. Biodegradation of the SR-PLLA material was even slower in an intraosseous environment than in subcutaneous tissue.

In the third experiment, bilateral unstable craniotomies were carried out in 20 lambs. For fixation, a non-reinforced, P(L/D)LA 96/4 stereocopolymer plate was used on one side, and a rigid titanium miniplate on the other side. The PLA96 plate was 0.4 mm-thick and flexible, and fixed in 10 lambs with rapidly resorbing SR-PGA miniscrews, and in another 10, with slowly degrading SR-PLLA miniscrews. During the follow-up time of two years, no complications were observed clinically or in magnetic resonance imaging, and the craniotomies were stable on palpation. Plain film radiography, histology and histomorphometry revealed incomplete consolidation of the 2.3 mm-wide craniotomy margins in all fixation groups. Bioabsorption of the SR-PGA miniscrews was rapid and transient osteolytic reactions were seen in the screw channels. The SR-PLLA miniscrews degraded in two years, but bioabsorption was incomplete. The PLA96 plate was completely absorbed in two years. Titanium plates tended to become translocated into the frontal sinus in the long term, and the fixed bone segments were thinner than on the PLA96-plated side.

The craniotomy lines in the first experiment were tested for tensile strength in 6 sheep at 6, 12 and 20 weeks. The SR-PLLA-plated specimens showed higher tensile strength than the titanium-plated specimens in 5 of 6 sheep, possibly as a result of more effective consolidation.

On the basis of the present results, the following conclusions can be drawn:

A craniotomy line in the calvarial membranous bone of young sheep consolidates very slowly by primary ossification and is vulnerable to the invasion of connective tissue. The consolidation process can be enhanced by a protective SR-PLLA plate, when compared with a narrow titanium plate, which results in non-union. An SR-PLLA plate is biocompatible when applied subperiosteally on sheep cranial bone, but it does not become absorbed in two years. The biodegradation process does not interfere negatively with bone regeneration. (I)

Consolidation of originally 2.3-2.5-mm wide craniotomy lines can be more reliably assessed by CT than by plain film radiography. Titanium plates and screws create artifacts and disturb detection of narrow non-union in CT, whereas SR-PLLA plates are completely radiolucent. (II)

SR-PLLA plates are very biocompatible in an intraosseous environment in calvarial membranous bone of growing sheep. Biodegradation process of SR-PLLA material is even slower in intraosseous than in subcutaneous tissue, and it does not interfere negatively with bone regeneration. (III)

A non-reinforced, flexible, wide PLA96 plate can be used for fixation of unstable, small craniotomies. Consolidation of a semirigidly fixed calvarial bone segment (PLA96 plate and SR-PLLA miniscrews) does not differ significantly from that of a rigidly fixed (titanium miniplate and screws) osteotomy. The biocompatibility of 0.4 mm-thick PLA96 plates is excellent, and they are absorbed completely in two years without negative effects on bone regeneration. (IV,V)

Both SR-PLLA and SR-PGA miniscrews can be used for plate fixation of pieces of cranial bone in growing sheep. As a result of a transient inflammatory and osteolytic reaction caused by rapid hydrolysis of PGA, a pure PGA implant is not as biocompatible as a pure PLLA implant, which causes a very mild foreign-body reaction. SR-PGA miniscrews lose their mechanical strength in less than four weeks, whereas SR-PLLA miniscrews appear to retain screw-holding power for up to six months. SR-PGA miniscrews are absorbed completely by 26-52 weeks, whereas SR-PLLA miniscrews are still undergoing biodegradation and bioabsorption at two years. (IV,V)

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